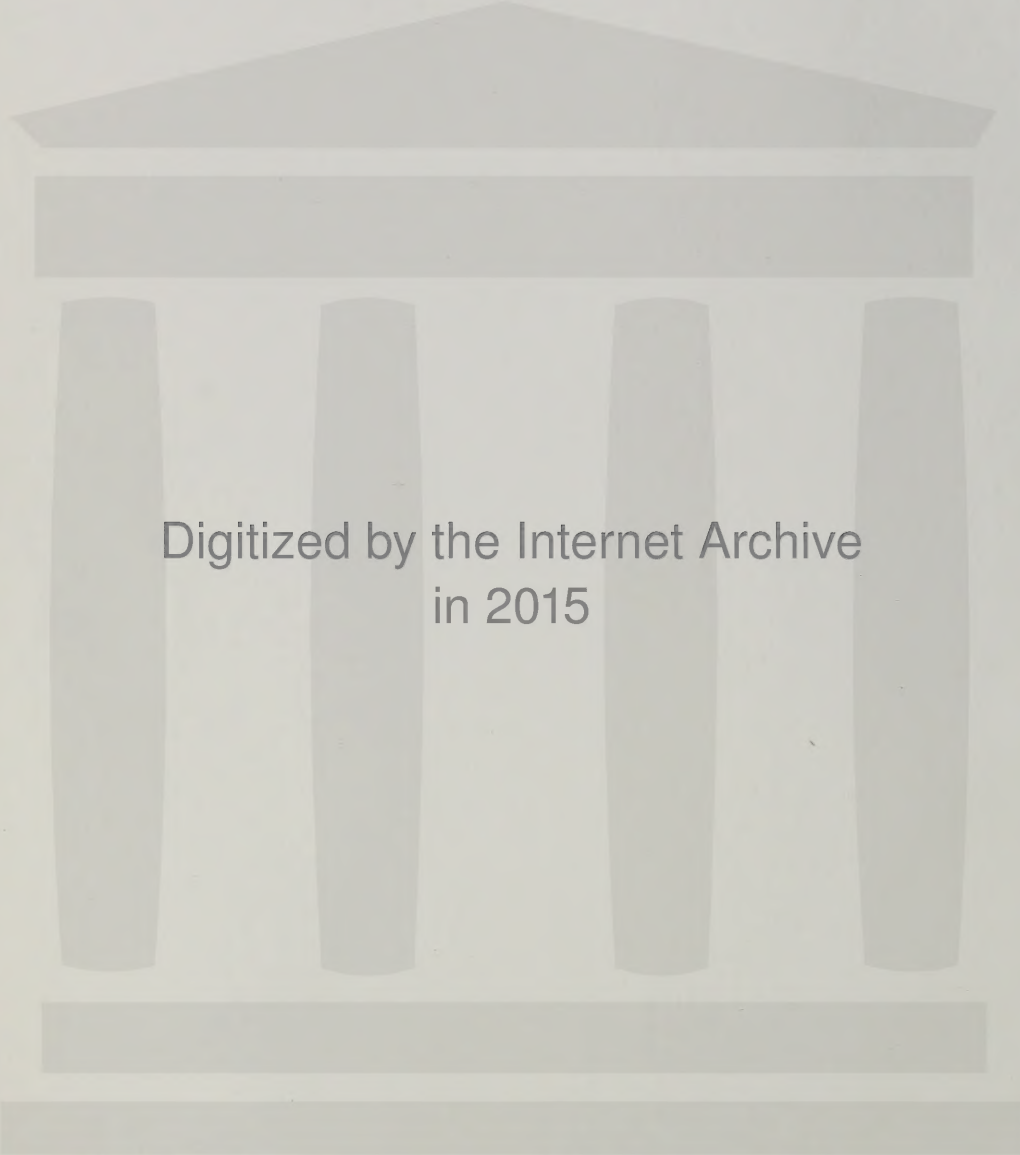


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Important Note: This drug is not a simple analgesic. Do not administer casually. Carefully evaluate patients before starting treatment and keep them under close supervision. Obtain a detailed history, and complete physical and laboratory examination (complete hemogram, urinalysis, etc.) before prescribing and at frequent intervals thereafter. Carefully select patients, avoiding those responsive to routine measures, contraindicated patients or those who cannot be observed frequently. Warn patients not to exceed recommended dosage. Short-term relief of severe symptoms with the smallest possible dosage is the goal of therapy. Dosage should be taken with meals or a full glass of milk. Substitute alka capsules for tablets if dyspeptic symptoms occur. Patients should discontinue the drug and report immediately any sign of: fever, sore throat, oral lesions (symptoms of blood dyscrasia); dyspepsia, epigastric pain, symptoms of anemia, black or tarry stools or other evidence of intestinal ulceration or hemorrhage, skin reactions, significant weight gain or edema. A one-week trial period is adequate. Discontinue in the absence of a favorable response. Restrict treatment periods to one week in patients over sixty.

Indications: Acute gouty arthritis, rheumatoid arthritis, rheumatoid spondylitis.

Contraindications: Children 14 years or less; senile patients; history or symptoms of G.I. inflammation or ulceration including severe, recurrent or persistent dyspepsia; history or presence of drug allergy; blood dyscrasias; renal, hepatic or cardiac dysfunction; hypertension; thyroid disease; systemic edema; stomatitis and salivary gland enlargement due to the drug; polymyalgia rheumatica and temporal arteritis; patients receiving other potent chemotherapeutic agents, or long-term anticoagulant therapy.

Warnings: Age, weight, dosage, duration of therapy, existence of concomitant diseases, and concurrent potent chemotherapy affect incidence of toxic reactions. Carefully instruct and observe the individual patient, especially the aging (forty years and over) who have increased susceptibility to the toxicity of the drug. Use lowest effective dosage. Weigh initially unpredictable benefits against potential risk of severe, even fatal, reactions. The disease condition itself is unaltered by the drug. Use with caution in first trimester of pregnancy and in nursing mothers. Drug may appear in cord blood and breast milk. Serious, even fatal, blood dyscrasias, including aplastic anemia, may occur suddenly despite regular hemograms, and may become manifest days or weeks after cessation of drug. Any significant change in total white count, relative decrease in granulocytes, appearance of immature forms, or fall in hematocrit should signal immediate cessation of therapy and complete hematologic investigation. Unexplained bleeding involving CNS, adrenals, and G.I. tract has occurred. The drug may potentiate action of insulin, sulfonyleurea, and sulfonamide-type agents. Carefully observe patients taking these agents. Nontoxic and toxic goiters and myxedema have been reported (the drug reduces iodine uptake by the thyroid). Blurred vision can be a significant toxic symptom worthy of a complete ophthalmological examination. Swelling of ankles or face in patients under sixty may be prevented by reducing dosage. If edema occurs in patients over sixty, discontinue drug.

Precautions: The following should be accomplished at regular intervals: Careful detailed history for disease being treated and detection of earliest signs of adverse reactions; complete physical examination including check of patient's weight; complete weekly (especially for the aging) or an every two week blood check; pertinent laboratory studies. Caution patients about participating in activity requiring alertness and coordination, as driving a car, etc. Cases of leukemia have been reported in patients with a history of short- and long-term therapy. The majority of these patients were over forty. Remember that arthritic-type pains can be the presenting symptom of leukemia.

Adverse Reactions: This is a potent drug; its misuse can lead to serious results. Review detailed information before beginning therapy. Ulcerative esophagitis, acute and reactivated gastric and duodenal ulcer with perforation and hemorrhage, ulceration and perforation of large bowel, occult G.I. bleeding with anemia, gastritis, epigastric pain, hematemesis, dyspepsia, nausea, vomiting and diarrhea, abdominal distention, agranulocytosis, aplastic anemia, hemolytic anemia, anemia due to blood loss including occult G.I. bleeding, thrombocytopenia, pancytopenia, leukemia, leukopenia, bone marrow depression, sodium and chloride retention, water retention and edema, plasma dilution, respiratory alkalosis, metabolic acidosis, fatal and nonfatal hepatitis (cholestasis may or may not be prominent), petechiae, purpura without thrombocytopenia, toxic pruritus, erythema nodosum, erythema multiforme, Stevens-Johnson syndrome, Lyell's syndrome (toxic necrotizing epidermolysis), exfoliative dermatitis, serum sickness, hypersensitivity angitis (polyarteritis), anaphylactic shock, urticaria, arthralgia, fever, rashes (all allergic reactions require prompt and permanent withdrawal of the drug), proteinuria, hematuria, oliguria, anuria, renal failure with azotemia, glomerulonephritis, acute tubular necrosis, nephrotic syndrome, bilateral renal cortical



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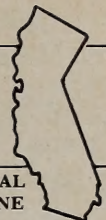
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Ototraumatic Effects of Hard Rock Music

RAYFORD C. REDDELL, PH.D., AND CHARLES P. LEBO, M.D.,
San Francisco

■ *Temporary and permanent shifts in auditory thresholds were found in 43 hard rock musicians and temporary shifts were also observed in some listeners. The threshold shifts involved all of the conventional puretone test frequencies. Custom-fitted polyvinyl chloride ear protectors were found to be effective in prevention of these noise-induced hearing losses.*

THE CORRELATION BETWEEN HIGH noise levels and potential cochlear damage is well established as is the predictability of hearing loss with intensive exposure to certain kinds and intensity of noise.^{1,2,3,4,5} Within the past few years, music produced by "hard rock" groups was added to those signals thought to be damaging to hearing.^{6,7,8,9,10,11,12} One of the authors participated in an analysis of rock establishment sound pressure levels which proved that the levels encountered in typical live amplified rock and roll music concerts exceed those considered safe for prolonged exposure. Reported herein is an evaluation of the hearing of rock musicians, measurements of the efficacy of ear protection for such persons, and observations concerning the temporary threshold shifts (TTS) produced by this musical sound energy output.

Method

Procedure. The Pacific High Recording Studio, to which we express gratitude, provided the authors with a mailing list of rock musicians who had used the studio's facilities for recording. Letters were sent to various performers requesting research participation, offering free otological examinations, audiological evaluations, and ear-molds to those interested. When possible, entire recording groups were scheduled for evaluation. Because of the variable availability of the subjects, interviews, otological and audiological evaluations were conducted at the recording studio, group "pad," rehearsal hall, or at the offices of the authors.

The audiological evaluations, which were preceded by a detailed otologic history and a standard otologic physical examination, included air conduction thresholds from 250 through 8000 Hz* and bone conduction thresholds through 4000 Hz. When testing was conducted at the

From the San Francisco Hearing and Speech Center and the Department of Otolaryngology and the Institute of Medical Sciences, Pacific Medical Center, San Francisco.

This investigation was supported by a grant from the Rosenberg Foundation.

Submitted June 17, 1971.

Reprint requests to: R. C. Reddell, Ph.D., San Francisco Hearing and Speech Center, 2340 Clay Street, San Francisco, Ca. 94115.

*The symbol for Hertz, which is the current designation of cycles per second.

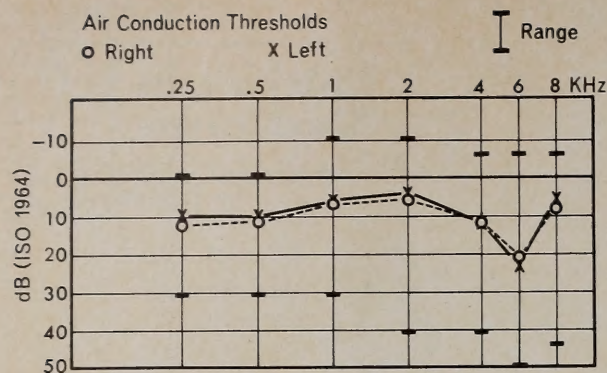


Chart 1.—Pure tone air conduction thresholds for 43 hard rock musicians.

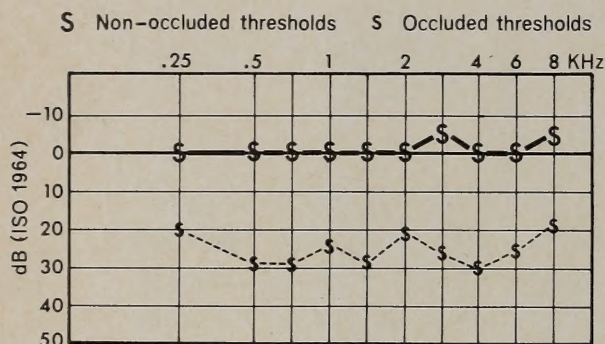


Chart 2.—Pure tone air conduction thresholds for normal hearing subject with and without ear protectors.

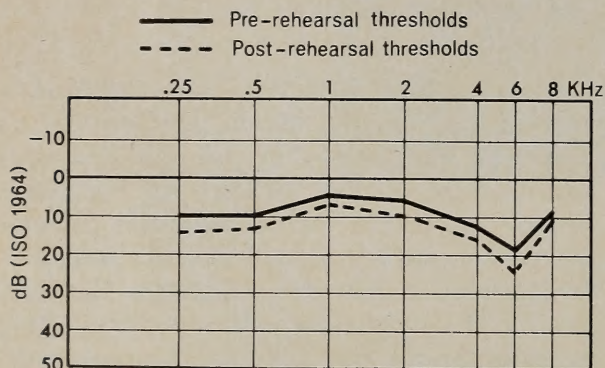


Chart 3.—Pre-rehearsal and post-rehearsal mean unilateral air conduction thresholds for seven subjects with earmolds.

audiologist's office, Allison Model 22 audiometers with TDH-39 phones were used in Industrial Acoustics Company sound-treated rooms. The subjects were tested at the recording studio and in the musicians' rehearsal settings with a portable Audiotone (Model AU-1) audiometer equipped with TDH-39 earphones which were housed in aural domes for maximum ambient noise attenuation.

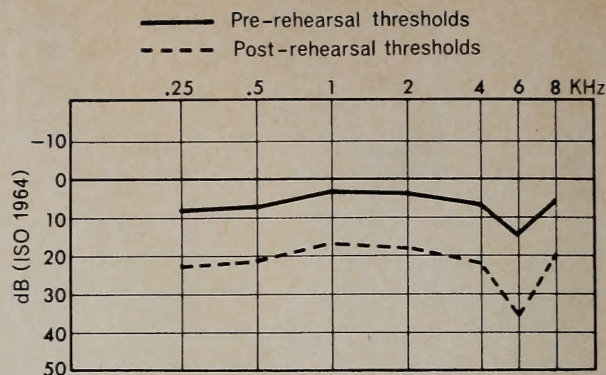


Chart 4.—Pre-rehearsal and post-rehearsal mean unilateral air conduction thresholds for seven subjects without earmolds.

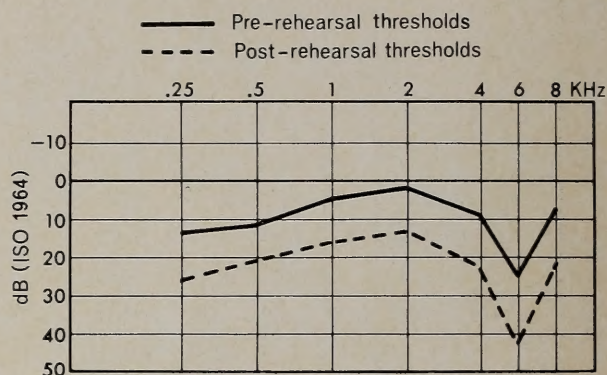


Chart 5.—Pre-rehearsal and post-rehearsal mean unilateral air conduction thresholds for four subjects without earmolds.

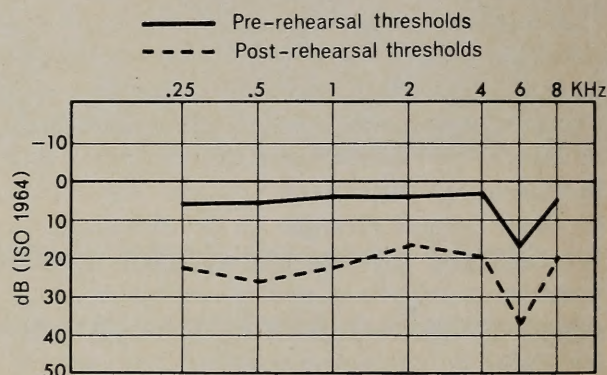


Chart 6.—Pre-rehearsal and post-rehearsal mean unilateral air conduction thresholds for two listeners.

Subjects. Of the 50 subjects originally included in this study, seven had to be excluded because of factors in their histories or physical findings that rendered them unsuitable. The mean age of the 43 subjects, 39 male, included in the data analysis was 22.02 years. The duration of exposure of amplified music ranged from one to six years; the last exposure to rock music before the testing varied between 12 and 72

hours. All subjects reported tinnitus following rehearsals and performances of their musical groups. Ten subjects said that they had chronic hearing difficulty, eight were uncertain, and the remaining 25 reported no subjective hearing loss. Six subjects had had previous experience with ear protectors.

Ear protectors. The State of California, Department of Industrial Relations, Division of Industrial Safety has published information regarding attenuation characteristics of commercial ear protectors.¹³ Since ordinary ear protectors were generally rejected by the subjects because they are rather conspicuous, the investigators provided non-perforated, polyvinyl chloride (marketed as "Dura-Flex") earmolds similar to those worn by hearing aid users. Being flesh colored and wholly contained within the external ear, they were acceptable to some subjects for clinical trial.

RTS. Seven subjects belonging to two musical groups participated in the threshold shift evaluations. In order to measure both RTS and the attenuation afforded by protection, the musicians were requested to select the earmold which seemed to provide the most comfortable fit and to wear that mold during rehearsal, leaving the other ear unoccluded. The musicians were requested to rehearse as they ordinarily would, playing their music with amplifiers set at their typical levels for periods of 105 minutes (usually with pauses of less than 2 minutes between selections, providing insignificant RTS recovery time). Audiological testing was conducted immediately preceding and following rehearsal.

Results

Hearing Acuity. Since none of the subjects had clinically significant air/bone gaps, the reported thresholds represent no conductive hearing loss elements. The mean pure tone air conduction thresholds (International Standards Organization [ISO] 1964) for the 43 subjects included in final analysis, shown in Chart 1, represents hearing within normal limits through 2000 Hz with a characteristic "notch" for higher frequencies below 8000 Hz. Of particular interest is the appearance of the greatest hearing loss at 6000 Hz rather than the more typical 4000 Hz. Also of interest is the slightly ascending audiometric configuration from 250 to 1000 Hz.

SISI Scores. Ten subjects who reported to the

audiologist's office for audiological evaluation were given Short Increment Sensitivity Index (SISI) tests at 6000 Hz, the frequency at which their loss was greatest. The mean threshold for these ten subjects was 22.0 decibels (dB, ISO 1964-hearing level). The mean SISI score was 82 percent, indicating cochlear pathologic change.¹⁴

Ear Protectors. One normal-hearing listener of the mean age of the experimental population was tested with earmolds identical to those made for the musicians. Free field non-occluded and occluded thresholds for this subject are shown in Chart 2. The curves demonstrate that the earmolds provide from 20 to 30 dB (reference: 0.0002 dyne per square centimeter) protection from 250 through 8000 Hz. These attenuation measurements are consistent with those of the better protectors tested by the Department of Industrial Relations of the State of California.¹³

RTS. Pre-exposure and post-exposure thresholds for the seven subjects who were fitted with earmolds are shown in Charts 3 and 4, demonstrating the effect of unilateral ear defender protection during typical rehearsals of two rock groups. The amounts of RTS in the occluded ears ranged from 1 to 5 dB; for the non-occluded ears from 12 to 18 dB. Analysis of these results by the sign test indicates significance at less than the .01 percent level of confidence.¹⁵

The results of pre-rehearsal and post-rehearsal exposure in another group of musicians are shown in Chart 5. Although both ears were tested, unilateral results are shown because the shifts for the two ears were virtually identical.

Listeners. Unilateral thresholds of two listener subjects tested before and after a 105-minute rehearsal are shown in Chart 6. (Again, the shifts for both ears were identical.) Of special interest is the occurrence of the same 6000 Hz "dip" which was seen in the musicians. The characteristics of the RTS of the listeners are comparable to those of the performers. It is difficult to subject test data for these limited numbers of listeners to statistical analysis for the purpose of describing variation in threshold shifts. Inspection of the raw data, however, reveals consistency among subjects in degree of RTS.

Discussion

That the music produced by the musicians included in this project produces temporary threshold shift is substantiated by these data; the prob-

ability of permanent hearing loss based upon the established relationships of TTS to irreversible cochlear trauma is thereby implied. It is recognized that definitive statements regarding permanent sensorineural hearing loss cannot be made from the mean threshold data for the 43 subjects reported in this study. As was stated previously, the 12 to 72 hours which elapsed for this population before its initial audiological evaluation is not an adequate recovery period for demonstration of permanent noise-induced hearing impairments. The SISI findings in ten subjects, however, are important implications for permanent hearing loss.

The protective efficacy of the mold-type ear defenders used in this study was also substantiated. Such protectors are not without their disadvantages. One of the groups observed that musicians wearing ear plugs tended to play louder. It would be foolish to preserve the hearing of four musicians and deafen an audience. These same musicians further reported the crescendo effect was only an initial reaction and that, by careful attention and experimentation, they were able to compensate for the presence of their earmolds.

Although this investigation did not include acoustical analysis of the music produced by the groups studied (this was previously reported^{8,9}), selective measurements of the sound pressure levels were made for each group and were found to be in agreement with those already published.

That the implications of this study for devotees of hard rock establishments are of special importance is shown by the data for the two listeners tested. Not only were the TTS exhibited by these two persons comparable to those shown by the musicians, but the pure tone patterns of their hearing thresholds were similar, including the 6000 Hz "dip" reported for the performers.

The uniformity of TTS across the frequency range tested warrants special consideration. Rock music contains considerable low frequency energy, causing tactile vibrations perceptible within the room in which it is produced. Morita¹⁶ reported that when ten subjects were exposed to 100 dB of white noise for 30 minutes while simul-

taneously being vibrated, the TTS was greater than if the 100 dB noise was used alone; and from this he hypothesized that the protective effect of the middle-ear muscles is reduced by vibration. The results of this study support Morita's hypothesis: The TTS was larger than might be expected in the low frequencies and the slightly ascending audiometric configuration from 250 to 1000 Hz was observed in the mean hearing thresholds for the experimental population. Factors other than the hypothesized vibration effect have not been excluded, however.

Several subjects expressed agreement with earlier opinions to the effect that as their musical idiom matures, the overall loudness will diminish. Whether or not this is dictated by the sequelae of high intensity output, the results are welcome.

The observations of this study substantiate the conclusions reported earlier: "Attenuation of the amplification to safe levels would substantially reduce the risk of ear injury in the audience and performers and, in the opinion of the authors, would still permit enjoyment of the musical material."⁸

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Neonatal Hearing Screening

LUCINDA BERNHEIMER, M.A., JACQUELINE KEASTER, M.SC., AND
F. H. LINTHICUM, JR., M.D., Los Angeles

■ *Auditory testing of neonates has received considerable attention in the last few years. As a result, several machines have been devised for this type of evaluation. It has been proposed that this equipment can be utilized by volunteer personnel to assess the hearing of infants. This investigation indicates that even trained audiologists are unable to make a definitive estimate of the hearing level in many newborns.*

OTOLOGISTS AND AUDIOLOGISTS have long been intrigued by the possibility of screening newborns for hearing. Proponents of routine mass screening cite two main reasons: Early diagnosis of hearing loss is a prerequisite for effective rehabilitation, and the newborn period offers a unique opportunity to work with a "captive audience" in hospital nurseries.

Investigators have generally dealt with two classes of response—physiological and behavioral. For determining physiological response, testers note the effects of a sound stimulus on heart rate,¹ respiration,² and electroencephalogram tracings.³ At first glance, such measurements may appear reassuringly objective. Question arises, however, as to whether measured changes constitute a response to the sound stimulus, or a response to the many internal stimuli operating in the neonate. Hardy⁴ noted that the newborn sleeps approximately 22 out of every 24 hours,

making it difficult if not impossible to catch him in an optimal state for testing.

Similar problems arise with the use of behavioral responses. Several studies have used gross behavior as response: Moro reflex, eye-blink, crying, cessation of crying and body movement.⁵⁻¹² Again, investigators must take neonatal instability into account. Certainly, without follow-up, it can only be said of the infants who "failed," merely that they did not respond to the stimulus.

Most published studies in the neonatal period have done little or nothing with follow-up. One exception was the study done by Hardy et al⁴ as part of the Collaborative Perinatal Project of 2000 infants. The criterion for hearing was a reflex startle response or some modification. In follow-up studies, Hardy found no positive relation between passes and failures and subsequent development of communication; and he concluded that testing during the neonatal period was without merit.

The personnel to be used as observers poses another problem in neonatal testing. One univer-

From Childrens Hospital of Los Angeles.

This study was made possible by a grant from the Research Study Club, Inc., of Los Angeles.

Submitted July 7, 1971.

Reprint requests to: F. H. Linthicum, Jr., M.D., Hearing and Speech Clinic, Childrens Hospital of Los Angeles, P.O. Box 54700, Terminal Annex, Los Angeles, Ca. 90054.

city medical center uses "trained volunteers."^{6,7} Another university-affiliated center advocates the use of "qualified audiologists" with three months' experience with newborns.¹¹ A report from a large hearing and speech center says that nurses, residents, or other physicians already working in the hospital nursery can be trained in a relatively short time to test the hearing of newborns routinely.¹⁰

Whoever the observers, they are subject to certain bias variables. Eisenberg¹³ cited the effects of observer position in relation to the infant and also observer fatigue as gauged by the number of infants studied and the time of day. A recent study by Ling et al¹⁴ supports Eisenberg's contention that observers exposed to an audible stimulus are biased toward judging any behavioral changes as response.¹⁵

In the past five years, the Hearing and Speech Clinic at Childrens Hospital of Los Angeles has had many queries concerning the desirability of setting up neonatal hearing screening programs in hospitals in the community. Because Childrens has no newborn nursery we had no experience in this field, and were further discouraged by our perusal of the literature.

We therefore welcomed the invitation by a staff neonatologist to do an exploratory project in a nearby hospital. We were granted permission to screen the newborns in the nursery without obtaining permission from individual physicians and without entering the results in charts.

At the outset, a number of questions were posed:

1. Can responses to an external stimulus—that is, sound—be reliably differentiated from responses to the many internal stimuli operating in the neonate?
2. What personnel should be used for testing?
3. How predictive are responses or non-responses in the newborn period?
4. Does the statistic that 1 in 2000 children is born with a hearing loss justify the time and expense necessary for setting up such a screening program?

Method

The population for the exploratory study consisted of 521 neonates ranging in age from a few hours to four days. Babies weighing less than 5½ pounds were considered premature and hence

were not included. The test group appeared to be a representative cross-section of all socio-economic groups in the community.

On the basis of comparative studies of available screening instruments done under sponsorship of the California State Department of Health,¹⁰ the Vicon Apriton was selected as the most satisfactory instrument. It has a broad band response from 100 through 6000 Hz, and a 3000 Hz tone. The intensity of both the broad band response and pure tone can be set at 70, 80, 90, and 100 decibels (dB).

Each infant was tested in his own bassinet in a far corner of the nursery away from the other infants. The speaker was held approximately 12 inches from the ear, and the sound presented for about 5 seconds (beginning with the broad band sound at 90 dB). Two observers made independent judgments of any response—its type and strength, the area of the body in which it occurred, and the pre-test state of the infant. Responses were not counted as such unless noted by both observers. Except for the eye-blink and the Moro reflex, behavior had to be repeatable in order to be considered a response. If there was no response to either the broad band or 3000 Hz tone at 90 dB, the intensity was increased to 100 dB.

To assess predictability, follow-up seemed a crucial part of the study. It appeared important to check for false negatives as well as for false positives. Hardy⁴ cited certain conditions, among them anoxic brain damage and hyperbilirubinaemia, that may not show their effects on hearing on the first or second day of life.

Parents of babies seen as neonates were invited to come to Childrens Hospital for a more definitive hearing evaluation when their babies were between three and four months old.

Results

Of the 521 neonates, 181 (35 percent) did not have response, by our criteria, to the screening in the nursery. The problem of discriminating between responses to sound and responses to various other stimuli proved to be a very real one. A hungry baby was so concerned with his animal desire for food that he rarely responded to the stimulus. Several subject variables were closely related to the incidence and type of response. Many of the non-responders, for example, had vernix caseosa still visible in the ear. The pre-test

state of the infant seemed to affect the nature of the response. The intensity of the response tended to decrease as the arousal of the infant increased. At the same time, we were impressed with the depth of sleep in many of our non-responders.

An attempt was made to correlate lack of response with various prenatal, perinatal, and post-natal factors, such as Rh-negative mother, heavy anesthesia during delivery, low Apgar ratings, cesarean sections, and respiratory distress during the first few hours of life. Examination of the charts revealed no general trends. Such factors tended to be evenly scattered between babies who responded and babies who did not.

In order to assess any factors which might be related to that particular nursery, permission was obtained to screen an additional group in a larger nearby hospital. Time did not permit screening a comparable sized group, but when 113 babies were tested a higher failure rate than reported by other investigators continued to emerge. From the total population of 634 subjects, 200 (32 percent) failed the screening.

Of the original 521 neonates, 147 were seen again between the ages of three and four months. They were tested in a sound field using voice and warbled pure-tone bursts from 500 Hz through 3000 Hz as stimuli. Of the 147, 145 passed without question, although 51 of these infants had failed in the nursery. There was some question about the responses of two babies, and they are being followed.

Five observers were used during the course of this project: two audiologists—one trained and experienced, the other trained and inexperienced; two graduate students in audiology; and one trained and experienced speech pathologist. Personnel trained in observation of hearing and speech are usually handicapped by a lack of experience with newborns, and need a period of practice observation. But after a month's practice there was still considerable disagreement among the observers as to type and strength of response. The situation could only be confounded by using volunteers.

Recommendations

On the basis of our experience, we cannot recommend a hearing screening program as a routine measure with a newborn population. The high number of false positives, together with the

statistic that 1 in 2000 children is born with a hearing loss, convince us that this is not a useful clinical procedure.

It is quite likely that our number of failures would have been sharply reduced had we gone back to re-test several times during the same day, or the next, or even taken the infant to a sound room to stimulate further. A screening program in operation in a university medical center does follow such a procedure. For the average community or small private institution, however, it is not feasible. While the cost of the equipment is not exorbitant, a great deal of professional time is necessary to conduct the program properly.

The lack of correlation between no response and various "suspect" factors indicates that there are subject variables operating in a newborn population which must be clearly defined before we can make assumptions based on gross behavioral observations. Proponents of mass neonatal screening argue that the newborn period creates a "captive audience" and is therefore the most logical time for diagnosis. More to the point, perhaps, is the questionable value of investigating the neonate routinely in any way.

In summation, we concur with a statement published by the American Academy of Ophthalmology and Otolaryngology in the *Perceiver* for December, 1970:

Review of data from the limited number of controlled studies which have been reported to date has convinced us that results of mass screening programs are inconsistent and misleading.

The academy goes on to say that it recognizes the need for the early detection of hearing impairments, but cannot recommend routine screening of newborns in the present state of the art. It urged, instead, increased research. The same sentiments were expressed by the American Academy of Pediatrics in the *Newsletter* of January, 1971, and by the American Speech and Hearing Association in *ASHA* of January, 1971.

If a valid and reliable technique for neonatal screening is found, a high-risk register can be used to locate infants whose hearing may be suspect at birth. In the meantime, the physician who comes into contact with the child during the first year of life is urged to look for indications of hearing loss. It is crucial that he have the right questions to ask the parents. He must learn to listen to the comments and descriptions of behavior made by mothers which might be signs of

abnormal hearing. Recently, a mother took her 11-month-old infant to an audiologist because she had come to notice that whenever she changed the baby's diaper he imitated her facial expressions but not her voice. This mother made a valid observation: her child did indeed have a hearing loss. Observations such as this remain a much more reliable diagnostic tool than any screening techniques yet available.

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HEART ATTACKS AFTER OPERATION

What are the odds of developing a heart attack before or shortly after anesthesia and surgery?

If you've never had a heart attack before, you stand about a one percent chance or less of developing one. In other words, you're no more likely to develop an attack with surgery than without it. If you do get a heart attack, the mortality rate is about 25 percent.

If you have had a previous heart attack, the probability of developing another one (either during the operation or in the first few days afterward) is six or seven times as great. If you have another attack, you're very likely to die of it. There's a 70 percent mortality instead of a 25 percent mortality.

The important factor seems to be the interval of time which elapses between the previous heart attack and the surgical operation. If the interval of time is very short, a matter of a few months, then the chance is very high that he is going to get a second heart attack. Often during recuperation from a heart attack the patient is advised to take a holiday. He may go away to a nice sunny place and then return home a month later the picture of health—bronzed and having put on a bit of weight. Then his doctor says, "Why don't you have those piles or that hernia taken care of before you go back to work?" The patient goes into the hospital to have a straightforward operation, gets his second coronary, and dies of it.

As the interval between the heart attack and the surgery is extended, the likelihood of another attack decreases. If the interval is as long as two to three years, the risk is probably no higher than if the patient had never had a heart attack at all.

—WILLIAM W. MUSHIN, M.D., Cardiff, Wales
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Diverticulum of the Vermiform Appendix

A Review of 28 Cases

LYLE N. YATES, M.D., Oakland

■ *Twenty-eight previously unreported cases of appendiceal diverticula were found in a 15-year retrospective review of records at five hospitals. The incidence is probably higher than is realized. Data drawn from the review indicated that the age of the patient and a history of previous attacks might be slight clues to distinguishing between diverticulum and acute appendicitis. Inflamed or not, rarely are these diverticula recognizable at the time of operation, but if the appendix is bulbous or club-shaped or there is increased thickening of the mesentery, the surgeon's suspicion should be aroused.*

In four of fourteen acute cases in the series, perforation had occurred—within 15 hours of the onset of symptoms in two cases. In four others there was abscess formation within the mesentery of the appendix.

DIVERTICULUM OF THE vermiform appendix is an uncommon but interesting problem. Few surgeons have a large number of cases in their personal experience. The diagnosis is seldom made before operation, and the condition may not even be recognized by the surgeon at the time of operation. Right colon resection has sometimes been done because of a mistaken diagnosis of carcinoma.¹ The purpose of this study is to call attention to diverticulum of the vermiform appendix and by so doing aid in its recognition at the time of operation.

Diverticula of the appendix can be divided into two distinct kinds. The first, extremely rare, is the true or congenital type, in which all layers of the wall of the appendix are found in the wall of the diverticulum. Such lesions are usually on the antimesenteric border and they may be single

or multiple. This type was completely reviewed by Everts-Sanarez in 1961.² The other type, more common, is the false or acquired diverticulum, in which the muscular layer is absent from the wall. Acquired diverticula are found along the mesenteric border, and they also may be single or multiple, but most often multiple.³

The etiology of diverticula of the appendix has been discussed in detail in the literature.¹⁻⁶ That of the very rare congenital type need not be discussed. The acquired type may develop from a weak point in the wall of the appendix along the side of a blood vessel. A scar from an old infection which causes a proximal obstruction may play a role, since diverticula have been brought about experimentally by increasing interluminal appendiceal pressure.^{1,5} Mucocoeles and other tumors may cause an obstruction³ which leads to formation of diverticula. Collins found mucocoeles in one-fifth of the cases reported.³ A pre-

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Reprint requests to: L. N. Yates, M.D., 3317 Elm Street, Oakland, Ca. 94609.

viously ruptured appendix may later appear as a diverticulum when mucosal regeneration occurs.⁷ It seems probable that there is more than one cause for the acquired type.

In a recent perusal of the surgical literature written in English, most of the reports found were of single cases or of ten or fewer. A review of the cross indexes, covering a period of about 15 years, in the pathology departments of several private and one county hospital in Oakland, California, turned up 28 previously unreported cases.* The hospital charts of these patients were reviewed and the following data compiled.

The age distribution is shown in Table 1. The average age of the 28 patients was 44.6 years. There were 14 men and 14 women. In 19 cases there was a single diverticulum and in nine more

than one. All were of the acquired type. In 14 cases the diverticulum or the appendix or both were found to be inflamed and probably causing the symptoms. In eight of the remaining 14 non-acute cases, the appendix was removed incidental to other surgical procedures. In one an appendectomy was performed because of recurring attacks, in one the appendix was subacutely inflamed secondary to a tubo-ovarian abscess, and in one the appendix was found to be nonacute without any apparent intra-abdominal disease to explain the patient's symptoms. In three cases the lesion was discovered at autopsy.

Table 2 summarizes the clinical and laboratory data in the 14 acute cases. All had either generalized, epigastric or right lower quadrant pain and all were given a preoperative diagnosis of acute appendicitis, with or without rupture. Even at operation the diagnosis of a diverticulum was not made. The closest to a correct operative diagnosis was made by one surgeon who stated it seemed as if there was an extra appendix present. In five cases the appendix was described as swollen and bulbous. Another surgeon described an abscess near the tip of the appendix and this was actually a diverticulum that had not ruptured. In two cases the appendix was described as having an unusual amount of induration and the mesentery to be decidedly thickened. In five cases the description of the appendix was consistent with acute appendicitis.

Perforation had occurred in four of the 14 cases—within ten hours of the onset of symptoms

*Peralta, Providence, Merritt, Children's Hospital of the East Bay, and Highland General Hospital (Alameda County).

TABLE 1.—Data on Age of 28 Patients with Diverticulum of the Appendix

Age Distribution (years)	Total	Acute	Other	Autopsy
1-10	1	0	0	1
11-20	0	0	0	0
21-30	3	3	0	0
31-40	9	6	3	0
41-50	6	2	3	1
51-60	3	1	2	0
61-70	3	0	3	0
71-80	1	1	0	0
81	1	0	0	1

TABLE 2.—Clinical and Laboratory Data in 14 Cases of Acute Diverticulum of the Appendix

	Age	Sex	Prev. Attack	Hours of Sickness	Loc. Pain at Onset	Tender-ness RLQ	RLQ Rebound Tender-ness	Nausea Vomiting	Bowel Habits	Temp.	Leukocytes per cu mm	Perforated
1.	42	F		12	Gen.	Epi. RLQ	No	Both	Reg.	99.2	13,700	
2.	34	F		48	Gen.		Yes	N		100.2	11,950	
3.	39	M	Yes	54	Peri-umb.	Yes	Very min.	N	Reg.	102.0	11,500	
4.	32	M	Yes	10		Yes	Yes	No		100.6	12,850	Yes
5.	53	M		20	Gen.	Yes	Yes	N		97.0	9,450	Yes
6.	23	M		48	Gen.	Yes	Yes	V		100.0	14,900	
7.	21	M	Yes	Days	RLQ	Yes	Yes	No		100.4	8,800	
8.	28	F	Yes		RLQ	Yes	Min.	No	Reg.	98.0	5,100	
9.	33	F	Yes	12	Gen.	Yes	Yes	No	Reg.	99.0	17,300	
*10.	76	F		Days	Gen.	Min.	No	V	Diarr.	96.0	24,000	Yes
11.	37	M		24	Peri-umb.	Yes	Yes	V	Reg.	98.8	14,500	
12.	31	M	Yes	24	Gen.	Yes	Yes	No	Reg.	99.0	10,800	
13.	47	M		15	Epi.	Yes	Yes	N	Reg.	100.2	11,650	Yes
14.	72	M		12	Epi. RLQ	Yes	Yes	No	Reg.	98.6	11,000	

*patient died

in one case and within 15 hours in another. In four others abscess formation was present within the mesentery of the appendix at the time of operation. The appendiceal lumen was obstructed in only one case and this was by a carcinoid tumor at the base of the appendix. There were no foreign bodies or mucocoeles in any of the 14 cases. A fecalith or soft fecal matter was found in the appendix in two cases.

The appendix was measured in all cases and was from 3.3 cm to 11 cm long and from 5 to 17 mm in diameter. The diverticula were from 1 to 10 mm in diameter, with an average of 4.8 mm in the 14 cases where recorded.

The treatment in all cases was appendectomy. Thirteen patients recovered without complication. One, a 76-year-old woman with a ruptured diverticulum, died of a massive upper gastrointestinal hemorrhage during the postoperative period. At autopsy a stress ulcer in the stomach was found to be the site of bleeding.

As was previously mentioned, the diverticulum was found at operation in 11 of the 14 non-acute cases and at autopsy in the other three. Nine of the patients were women, five were men. The diverticulum was not a contributory factor in the death of any of the patients. The average age of the 11 patients with diverticulum diagnosed at operation was 49.6 years. In eight cases appendectomy was incidental to other surgical procedure—a hysterectomy in five, and sliding hernia, carcinoma of the right colon and a partial obstruction of the small bowel in the other three. Classification of the appendix in three cases in which the operation was primarily appendectomy was "interval appendix" in one case, subacute in one, and nonacute in one.

In none of the 14 nonacute cases reviewed was there history of gastrointestinal symptoms related to the presence of the diverticulum. The gross appearance of the appendix was not mentioned in the operative notes in four of the 11 nonacute cases. In two cases the appendices were described as being bound down by adhesions, and in two cases it was noted that the appendix was firm and short. One appendix was described as showing signs of chronic inflammation, and one was observed to be bulbous with a thick mesentery. Rupture of the tip of the appendix was seen by the surgeon in one case. From review of the charts it appeared there were no complica-

tions from the removal of the appendix in any of the nonacute cases.

Discussion

The diagnosis of diverticulum of the appendix in the non-infected state is rare, for the lesion then causes no symptoms. Very infrequently such a lesion can be demonstrated radiographically.^{7,8}

When a diverticulum becomes infected the signs and symptoms are usually those associated with acute appendicitis. A perhaps distinguishing note is that in six of the 14 acute cases in this study there was history of previous attacks. And another point of distinction is that the average age of patients is greater than that of those with acute appendicitis. The clinical course is similar to that of acute appendicitis, although early perforation as was noted here has been observed before.¹ In the present study perforation was found in a high proportion of cases—four of fourteen. There was abscess formation within the mesentery in four others.

Although recognition of a diverticulum at operation is difficult, it is probably not impossible if the surgeon keeps the condition in mind enough to be suspicious on finding a bulbous or club-shaped appendix with a pronounced thickening of the mesentery. With such clues, mistaken diagnosis of neoplasm might be avoided.

Treatment is surgical removal with appendectomy. If appendiceal diverticulum were fortuitously recognized in the course of a surgical procedure being carried out for some other reason, appendectomy then and there would seem advisable in light of the danger of early perforation. This was done in all eight cases of fortuitous discovery in the series here reviewed.

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The Apexcardiogram in Ischemic Heart Disease

HOWARD H. WAYNE, M.D., San Diego

■ *The apexcardiogram (ACG), when recorded serially in patients with acute myocardial infarction (AMI), preinfarction angina (PIA) and stable ischemic heart disease (IHD), appeared to reflect the abnormal patterns of contraction of the left ventricle in these conditions. Thus, paradoxical bulging (dyskinesis) of the systolic wave or increased "a" wave amplitude with gradual recovery over several weeks was found in all 60 patients with documented AMI and in 18 of 20 patients with PIA. Electrocardiogram changes were noted, however, in only eight of the PIA patients. Changes in the ACG frequently antedated ischemia in the ECG. Paradoxical bulging of the systolic wave of the ACG was additionally noted in patients during the pain of angina pectoris but this promptly disappeared after the administration of nitroglycerine. Patients with classic angina often had normal resting ECG's but abnormal resting ACG's.*

In contrast to the relatively transient abnormalities noted above, the ACG remained unchanged in most patients with stable IHD during follow-up of three months to two years. Patients undergoing coronary bypass operations, however, showed immediate improvement in the ACG in the postoperative period.

These results suggest the ACG reflects the contractile pattern of the left ventricle, and may be an indirectly recorded ventriculogram. Its enhanced sensitivity and the earlier development of changes in comparison to the ECG make this a valuable tool in the study of patients with heart disease.

IT IS A COMMON clinical observation that ischemic heart disease (IHD) may exist in advanced form without clinical manifestations; indeed even in the presence of symptoms a definitive diagnosis is often difficult. Although most physicians, when confronted with classic angina pectoris, feel rea-

sonably secure in their diagnosis even without additional clinical support, they are less certain when pain or other symptoms are atypical. Pity, therefore, the asymptomatic patient with IHD, examined routinely with just a stethoscope and resting electrocardiogram (ECG) and pronounced "well" so far as his heart is concerned when no abnormalities are detected.

Unfortunately the insensitivity of the usual tools—that is, the stethoscope, the resting ECG, and even the exercise ECG—is not generally ap-

From the San Diego County Heart Center at the Donald N. Sharp Memorial Community Hospital.

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Reprint requests to: H. H. Wayne, M.D., 2290 Sixth Avenue, Suite 203, San Diego, Ca. 92101.

preciated. This is perhaps why half of all deaths from acute myocardial infarction (AMI) are reported to occur in persons with no previous clinical heart disease¹ and why 25 percent of all AMI's are "silent" or atypical.^{2,3} Coronary cinearteriography is, of course, the definitive test. Even so, discrepancies often exist between the clinical features and the cinearteriograms.^{4,5} Additionally, coronary cinearteriography is neither routine nor practical to perform serially, nor is it universally available.

These problems are possibly prime reasons why many patients who are to have an AMI are not identified, in spite of warning symptoms for one to two months,^{6,7} and perhaps why 60 to 70 percent of all deaths occur before they reach a hospital.⁸⁻¹¹ Conceivably, if earlier detection of IHD or an approaching infarction were possible, corrective measures or prophylactic medication could be instituted.

There is promise that such early identification may be possible through study of the apex impulse. Harrison, Dimond and others¹²⁻¹⁸ have long emphasized the usefulness of precordial palpation, and numerous precordial graphic recording techniques for studying the apex movement have been described.¹⁹⁻²⁵ The best known of these techniques, the use of the apexcardiogram (ACG), is relatively simple to do. Its ability to reflect both systolic and diastolic events in the cardiac cycle as well as hemodynamic changes has been extensively documented.²⁶⁻³⁸ Close correlation between abnormalities of the systolic contraction wave (scw) of the ACG and abnormal left ventricular wall motion—that is, dyskinesis, akinesis and asynchrony—have recently been confirmed directly with ventriculograms and cinefluoroscopy.³⁹⁻⁴³ Since it is recordable at the bedside or in the office, is non-invasive, and can be obtained serially in the same patient, its use in the study of patients with IHD appears promising.

It is the purpose of this paper to review some of the graphic changes we have seen in the ACG in normal persons and in patients with IHD from our study of approximately 3000 ACG's in 600 patients during the past five years. Preliminary studies have been described previously⁴⁴ and more detailed information is to be reported elsewhere.⁴⁵ Emphasis in this paper, therefore, will be on simple description of the wave form changes in various phases of IHD.

Methods

There were 215 normal persons with no history, physical findings, ECG or phonocardiographic evidence of heart disease. Ages ranged from 20 to 60 years. There were 325 patients with documented IHD based upon a classic history of angina pectoris, or an abnormal electrocardiogram (ECG) reflecting either an old myocardial infarction or significant ST segment depression. Ages ranged from 35 to 80 years. One hundred and thirty of these patients were followed serially for three months to two years. An additional 60 patients with documented acute myocardial infarctions were also recorded and followed serially.

Method of recording the ACG. This has been described in detail and is being reported elsewhere,⁴⁶ and therefore will be outlined only briefly here. The patient was placed in the lateral decubitus position; the exact center of the apex impulse was marked, and the apex pick-up was strapped precisely over this area. We have found the end-piece of a B-D Fleischer stethoscope with the diaphragm removed to be the most convenient pick-up to use. It is flat, is easily positioned and does not create artifacts as other pick-ups do.⁴⁶ Using adaptors and approximately ten inches of rubber tubing, the pick-up was connected to a pulse wave transducer (a Hewlett Packard 374 or 21051D and a Siemens calibrated transducer were used in this study). This in turn was connected to a suitable recorder. Although most of the tracings in this study were obtained on a four or seven channel Elema Schonander Mingograf, at times recordings were made on a single channel Sanborn series 500 ECG or the Sanborn Twinbeam Phonocardiograph. In general, a simultaneous ECG, carotid pulse tracing (CPT) and phonocardiogram (PCG) were obtained along with the ACG.

Since positioning of the ACG pick-up is critical, displacement after its release because of movement of the underlying skin from pull created by the rubber strap had to be carefully avoided, lest artifactual recordings could result. Oscilloscopic monitoring before the recording considerably facilitated proper placement. In addition, once positioning was achieved, care had to be taken to avoid patient rotation, since this too could alter the wave form.

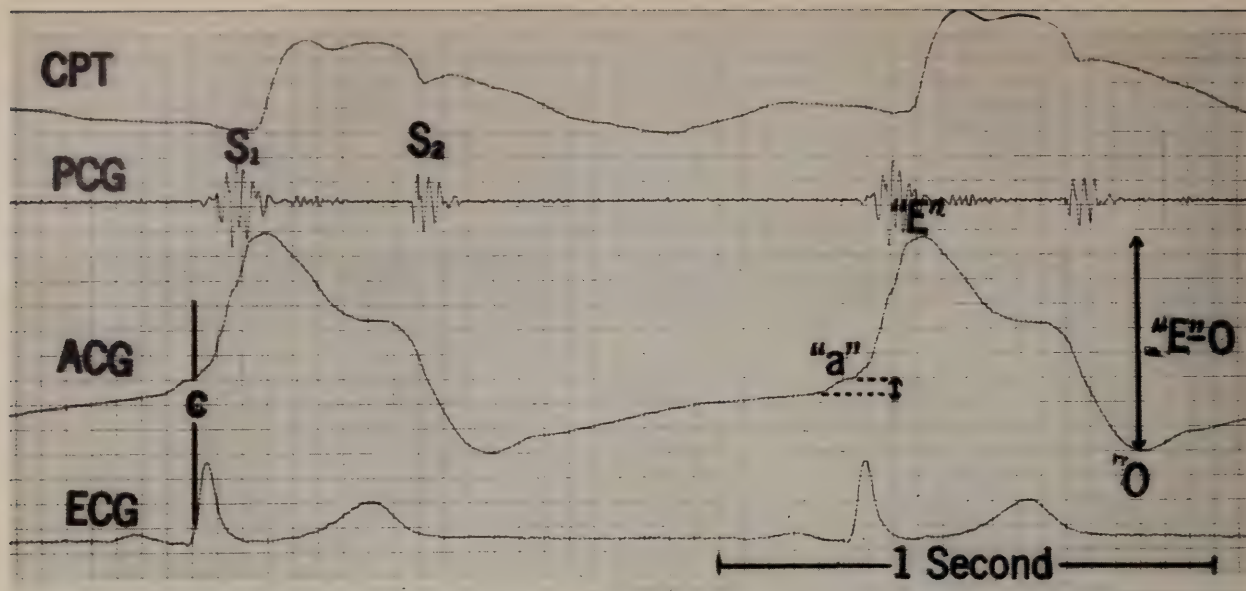


Figure 1.—The normal apexcardiogram (ACG). Note the acute downslope of the systolic wave beginning with the onset of ejection (E point) with a change in slope in the latter part of systole. The atrial filling wave ("a" wave) is quite small in amplitude in comparison to the vertical amplitude of the entire wave (E-O). Additional abbreviations: CPT= carotid pulse trace, PCG= phonocardiogram, ECG= electrocardiogram, O= opening of mitral valves, S₁= first heart sound, S₂= second heart sound, C= onset of ventricular contraction.

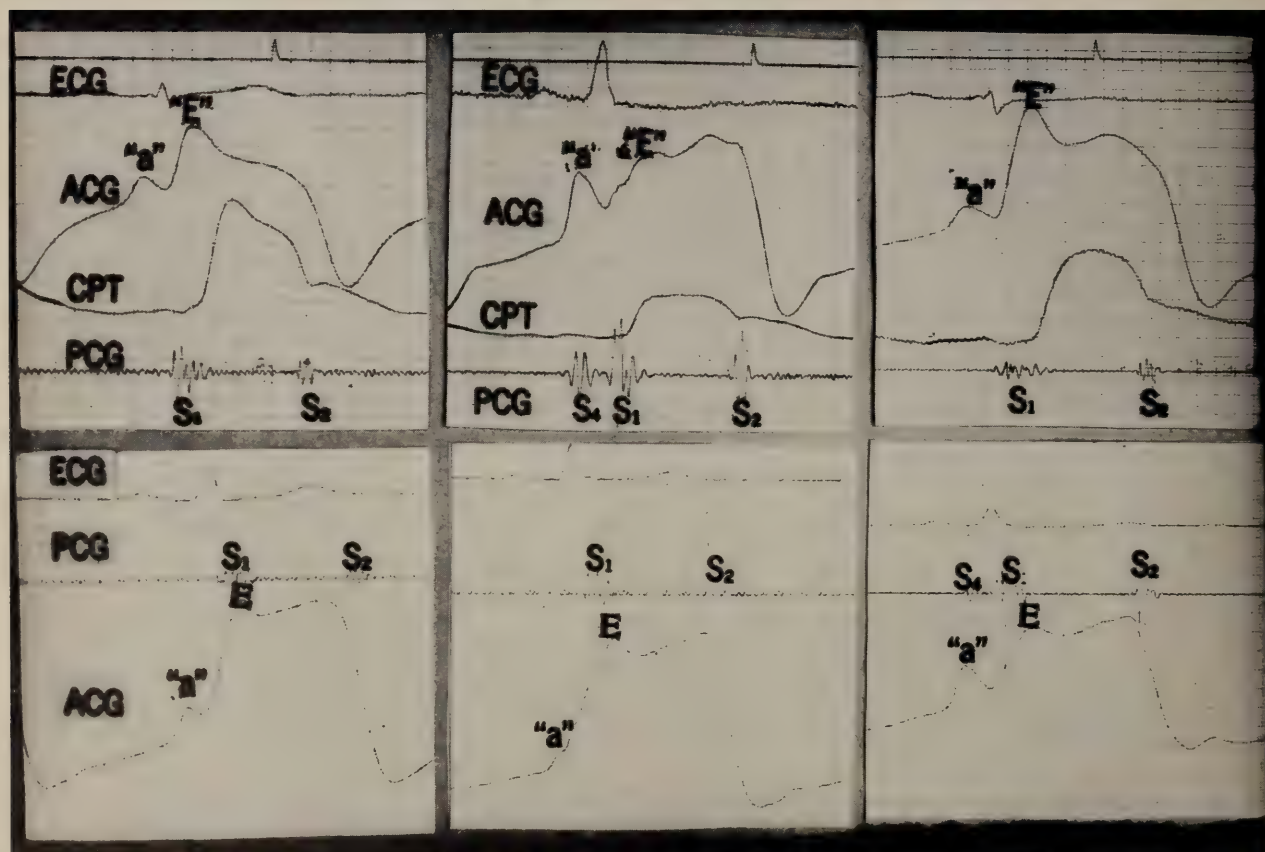


Figure 2.—ACG's recorded from patients with ischemic heart disease. In comparison to Figure 1 note the much larger "a" wave, a change in downslope angle of the systolic wave before midsystole to be followed by a more gradual downslope (top left), a paradoxical bulge (top, center and lower three strips) or a sustained wave (top right). Abbreviations: same as Figure 1.

Results

The normal ACG. Figure 1 shows an ACG recorded from a normal subject along with a simultaneous ECG, CPT and PCG. The initial upward deflection represents ventricular filling due to atrial contraction and is called the "a" wave. Its total amplitude was usually less than 10 percent of the entire systolic contraction wave (scw) and its duration in 166 normal subjects was 64 ± 11 msec.

Beginning usually just before the peak of the R wave of the ECG, is a sharp upstroke (point C) signifying the onset of ventricular contraction. Note the onset of this upstroke begins on a horizontal plane above the onset of the ascending limb of the "a" wave. It is to be emphasized that the onset of the ventricular upstroke should not occur below the level of the onset of the "a" wave. The finding of such a "negative" wave means erroneous placement of the ACG pick-up, with resultant artifactual recordings.⁴⁶

The ventricular upstroke reaches its own peak (E point) at the time of opening of the aortic valves shortly after mitral and tricuspid valve closure (S_1). At the onset of ejection, represented by the beginning upstroke of the carotid pulse tracing, there is an acute downstroke of the normal scw of the ACG with a change in contour of the downslope beginning about mid-mechanical systole (interval between the first heart sound (S_1) and the second sound (S_2)).

Figure 2 shows a series of ACG's recorded from creased in both amplitude and duration and, patients with IHD. The "a" wave is frequently in-when abnormal, is often a reflection of elevation of the left ventricular end diastolic pressure,³⁵⁻³⁸ or increased left atrial filling pressure.

Distinct differences are noted as well in the scw. The downslope is much more gradual; it may be sustained throughout systole or even may be paradoxical in direction. A change in contour of the downslope is often noted well before mid-mechanical systole. Such abnormal patterns of the downslope of the ACG probably represent external reflections of dyskinesis, akinesis, and asynchrony commonly noted in ventriculograms of patients with IHD. The scw of the ACG, whether normal or abnormal, will remain stable when repetitive tracings are taken over a period of months to years, as long as technically proper

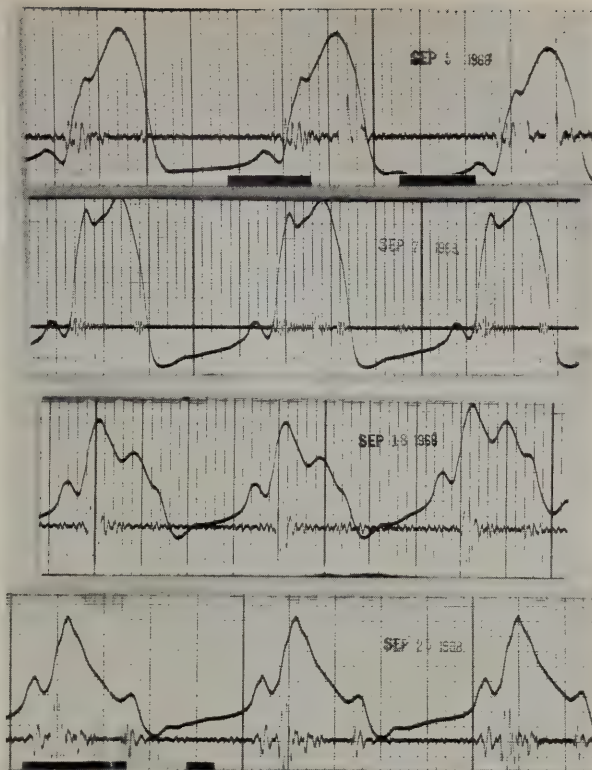


Figure 3.—Serial ACG's in a 62-year-old patient with an acute myocardial infarction whose initial ECG failed to show diagnostic changes. Note the pronounced paradoxical bulge in the initial recording with gradual recovery. Note too the increasing "a" wave amplitude with the development of a fourth heart sound.

recordings are obtained, and the patient's disease remains stable.⁴⁶

The "a" wave duration in 215 patients with IHD was 73 ± 20 msec. Because of abnormal skewing of the data in IHD patients and in normal controls, using a standard "t" test, the differences between the means were significant ($P < .0005$).

Changes in Acute Myocardial Infarction. Figure 3 shows representative serial ACG's recorded in a 62-year-old man who had had myocardial infarction eight years previously and had remained asymptomatic for the next six years. On the morning of his admission to the hospital he had mild chest pain similar to that experienced during his first heart attack, and lasting about one hour. The symptoms were not accompanied by autonomic nervous system phenomena. The patient was seen three hours later and an electrocardiogram revealed only evidence of an old inferior wall infarction. The initial ACG is seen in the upper strip of Figure 3 and pronounced paradoxical bulging of the scw is clearly evident.

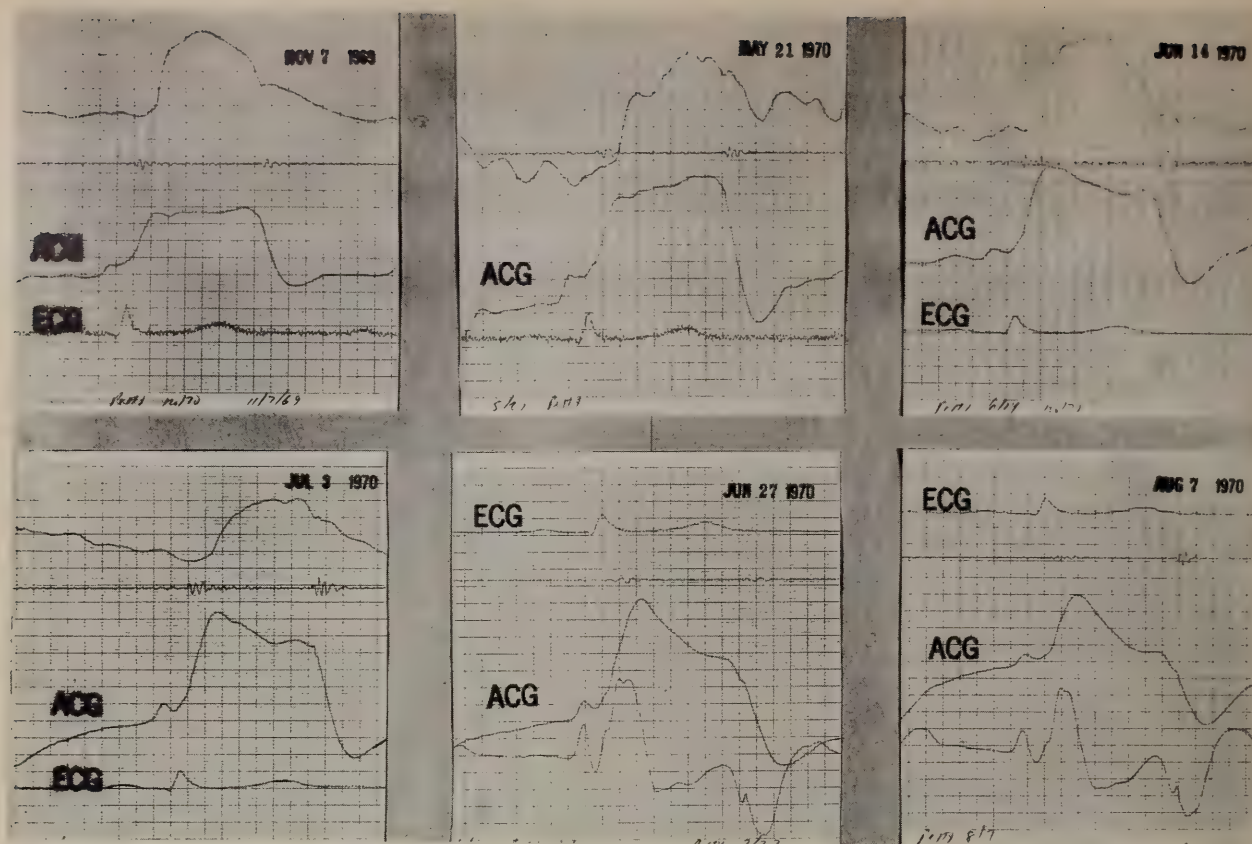


Figure 4.—Serial ACG's in 65-year-old patient with pre-infarction angina. Note the development of a paradoxical bulge and increased "a" wave amplitude in the recording of May 21 in comparison with November 7 when the patient was asymptomatic. Gradual recovery is seen in the follow-up recordings.

The patient reluctantly followed a recommendation of immediate admission to hospital. An hour later, while he was in the emergency room awaiting admission, cardiac arrest took place. He was successfully resuscitated. The serial changes in the scw may be noted along with a large "a" wave presumably secondary to loss of ventricular compliance. The paradoxical bulge diminished gradually during the stay in hospital. The day following admission, evidence of a new inferior wall infarction was seen on the ECG and there was moderate enzyme elevation. Subsequent recovery was uneventful except for mild congestive heart failure. A fourth heart sound coinciding with the "a" wave is seen best in the bottom strip of Figure 3.

It is common knowledge that the initial ECG may fail to show changes during the early hours and even days of an acute infarction. It has been our experience that the ACG is almost always abnormal at the onset of an infarction and changes progressively during the first several days.^{44,45} Interestingly, paradoxical bulges of the scw as

well as an "a" wave of increased amplitude were noted regardless of whether the infarction was inferior, anterior or subendocardial. It would seem that the abnormal wall motion occurring during an acute infarction, whatever its location, was transmitted in some manner to the apex impulse.

Transient abnormalities were often seen in the presence of simple myocardial ischemia when the ECG showed only T wave changes. This suggests the ACG may be more sensitive in detecting left ventricular dysfunction. Similar findings have been noted by other investigators, in that abnormalities of the precordial impulse frequently antedate other evidence of left ventricular disease.^{47,48} The importance of this cannot be over-emphasized since the ECG provides anatomical and not functional information. More complete details will be reported separately.⁴⁹

Pre-infarction angina. Figure 4 shows serial tracings in a 65-year-old woman who had symptoms highly suggestive of pre-infarction angina. She described increasing fatigue, dyspnea on ex-

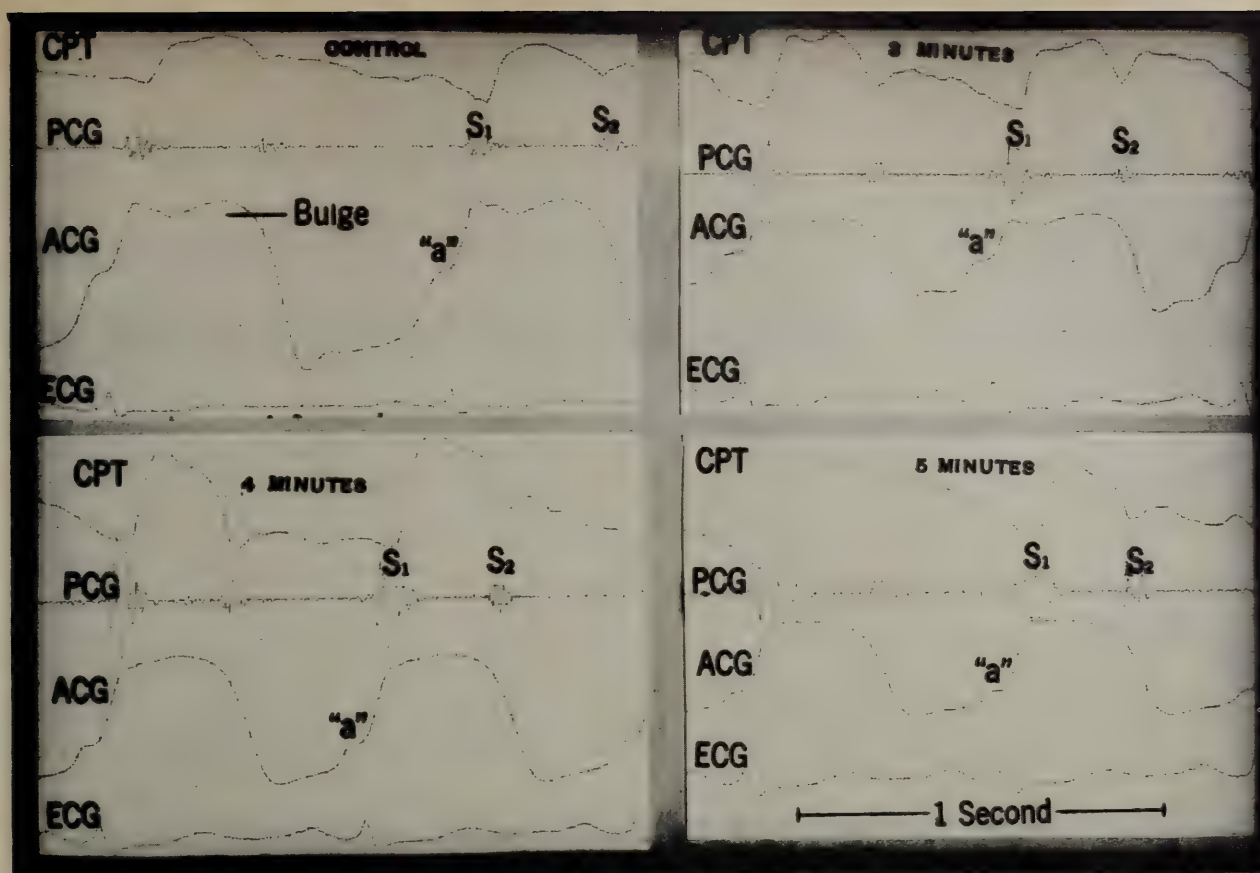


Figure 5.—Serial ACG's during angina pectoris with recovery following nitroglycerine administration. Note the giant "a" wave and bulge of the systolic wave initially.

ertion, palpitation and angina pectoris. Of great significance was the fact these symptoms were not volunteered, indeed were actually denied in written answers to questions on the history form and only came to light on close re-questioning of the patient after the apexcardiographic changes of May 21. Serial ACG's in the months preceding May 21, although abnormal as shown in the recording of 7 November 1969, had remained stable. Note in the tracing of May 21, that the "a" wave amplitude, expressed as a relative percentage of the entire scw, had gone from 13 percent on November 7 to 24 percent on May 21 while the scw now showed a distinct paradoxical bulge that could not be eliminated despite repeated repositioning of the ACG pick-up and rotation of the patient. Subsequently, the patient admitted to the new development of the above symptoms but said she had attributed them to "old age." The progressive improvement of the ACG in the ensuing weeks is evident. It was characterized by a reduction in the amplitude of the "a" wave, loss of the paradoxical bulge, and improvement in the downslope of the scw. Serial ECG's during

this period all remained within normal limits. Coinciding with the improved ACG was a gradual disappearance of the previously noted symptoms. In a series of 20 such patients with characteristic pre-infarction angina, only eight (40 percent) showed changes in their ECG while all 20 showed progressive changes in their ACG similar to the change depicted in Figure 4. In contrast to acute infarction, the ACG changes in pre-infarction angina occurred over a more prolonged period.

Changes Noted in Angina Pectoris. Figure 5 shows serial ACG's obtained from a 60-year-old man during angina. The patient had documented occlusion of the right coronary artery, 90 percent occlusion of the left circumflex and a ventricular aneurysm. Notable in the initial strip was a giant "a" wave as well as significant paradoxical bulging of the scw. Beginning about three minutes after the sublingual administration of nitroglycerine, reduction in the amplitude of both the bulge and "a" wave was seen. By five minutes, "a" wave amplitude had been reduced from 39 percent to 15 percent. The scw, although still abnormal, showed loss of the bulge. These serial

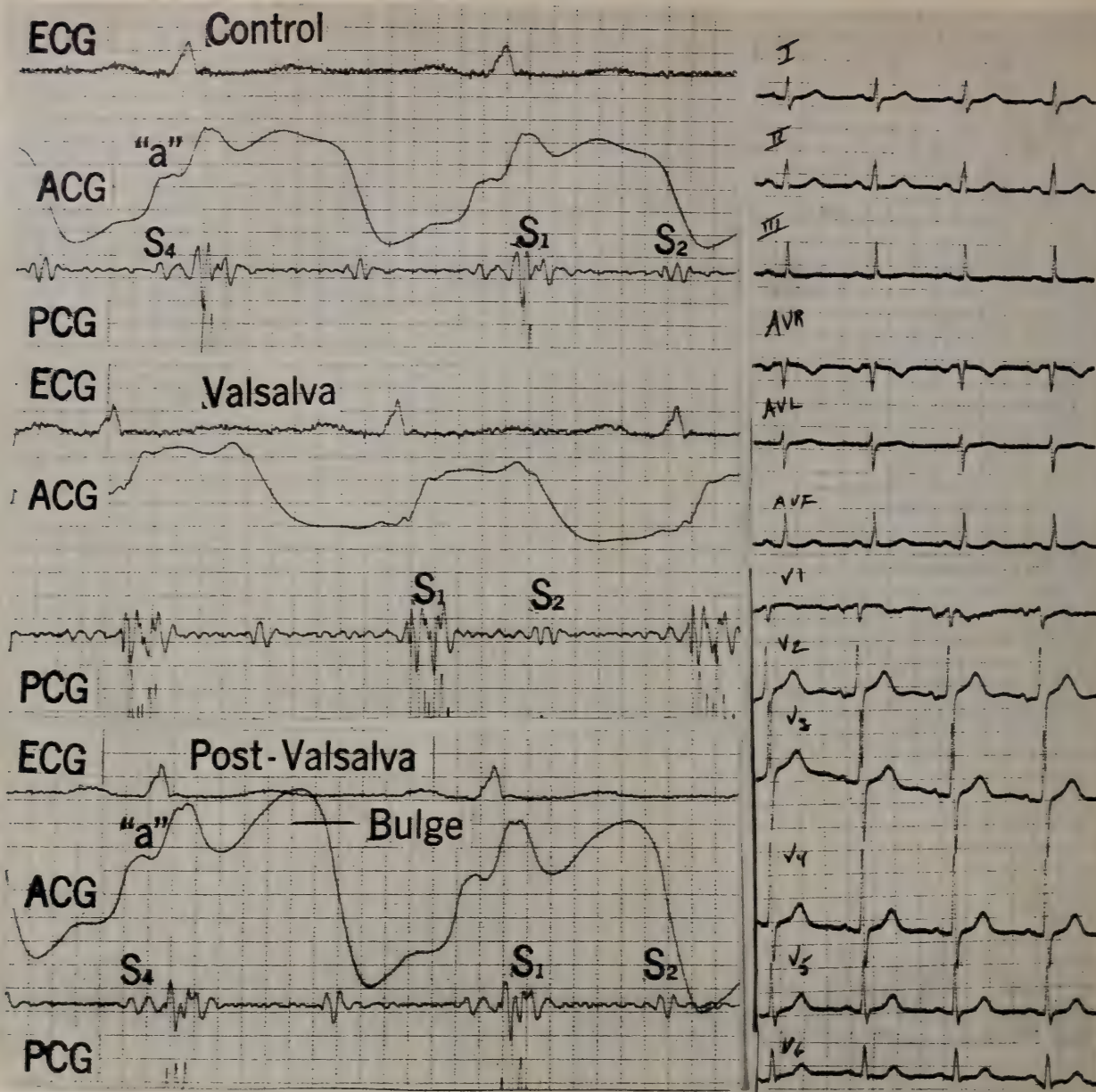


Figure 6.—ACG recorded in a 55-year-old man with unsuspected heart disease. Note the disappearance of the large "a" wave, bulge and S_1 during the Valsalva maneuver, with intensification immediately on recovery. The EKG on the right, taken a few moments later, was normal.

tracings were obtained without movement of the ACG pick-up or rotation of the patient.

Although the presence of disease was later confirmed in this patient by direct cardiac catheterization, it is reasonable to assume that serial changes in the ACG, similar to those described in Figure 5, in the absence of patient rotation and apex pick-up displacement, are acceptable documentation of changing left ventricular function compatible with the hemodynamic changes occurring in angina pectoris.

In our serial studies of patients with IHD, para-

doxical bulges were often noted in patients during angina. Commonly, patients would show the presence of a bulge before the development of pain, but often no word of pain would be volunteered or even given in reply to specific questioning. The use of nitroglycerine during these episodes would cause prompt abatement of these abnormalities within the space of a few minutes. The resting ECG was normal in 12 of 30 patients who had frequent angina pectoris—several times a day or week. In contrast, the resting ACG was considered abnormal in all 30 patients.

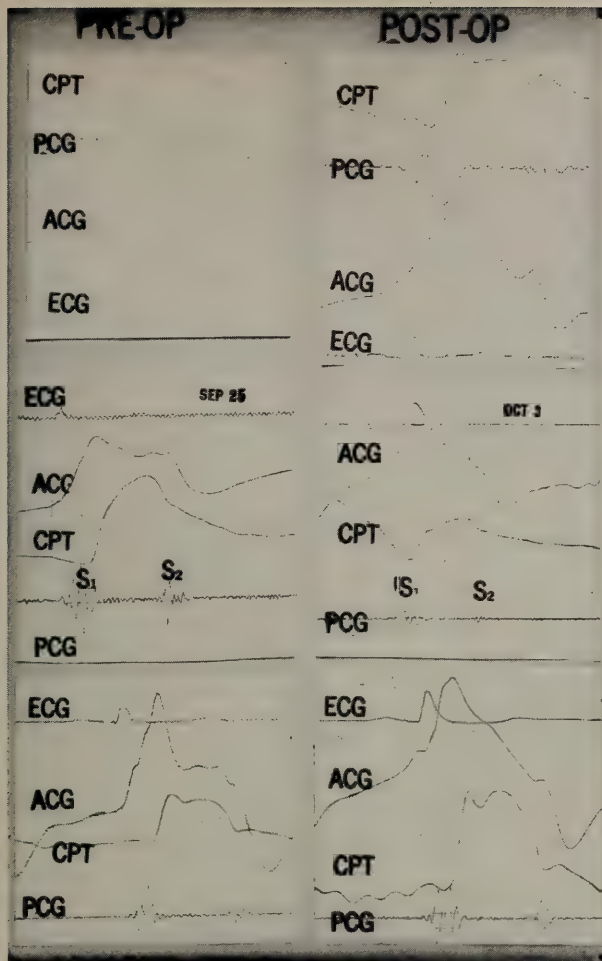


Figure 7.—ACG's before coronary by-pass operation (left hand strips) and after operation (right hand strips) in three patients. Note improved systolic wave in the postoperative tracings.

Another method of identifying abnormalities of left ventricular wall motion is seen in Figure 6. The patient, a 55-year-old man, was known to have mild diabetes, controlled with oral agents, but was otherwise reported to be in good health. A recent complete physical examination by an internist and an ECG had disclosed no abnormality. The initial recording in the top strip of Figure 6 shows a very large "a" wave, a paradoxical bulge of the scw and a high frequency fourth heart sound (recorded up to 100 Hz). A Valsalva maneuver caused pronounced reduction in all three abnormalities. Upon Valsalva release, striking intensification of all abnormalities took place. An ECG taken immediately after release was entirely normal. Interestingly, no chest discomfort was experienced by the patient although apprehension was evident. Again, it is reasonable to assume that when such changes occur as part of

a serial sequence, abnormal left ventricular function may be presumed to be present.

Pre-Coronary and Post-Coronary By-pass Changes. Figure 7 shows tracings of three patients with documented IHD, established by coronary cinearteriography, and considered surgical candidates for a by-pass graft. The strips show the pre-operative abnormalities and tracings taken shortly after corrective coronary by-pass operation was successfully carried out in each patient. The improvement in the scw of the ACG consists of replacement of the paradoxical or sustained contraction wave by a rapid downslope throughout all of systole. In each instance the improved ACG was associated with loss of angina, easy fatigability and other symptoms present prior to surgery.

Discussion

Convincing data now seems to be present that the ACG is a sensitive indicator of the abnormal left ventricular wall function known to be present in most patients with ischemic heart disease. Since abnormal myocardium contracts at reduced velocity while maintaining an elevated wall tension,⁵⁰ the slower downslope of the abnormal ACG appears to reflect this reduction of velocity. Similarly, paradoxical bulging of the scw apparently reflects paradoxical wall motion.⁴⁰ Initially, normal and abnormal myocardium both begin their shortening simultaneously; however, normal myocardium presumably completes its contraction phase first, apparently before mid-systole, while the slower, abnormal myocardium is still shortening. That is to say, abnormal myocardium contracts out of phase (asynchrony).⁵¹ This perhaps explains the abrupt change in contour of the scw of the ACG before mid-systole in the abnormal patient. It is possible, therefore, that the ACG reflects the moment to moment contactile pattern of the left ventricle. In other words, it appears to be an externally recorded, reciprocal analog curve of a ventriculogram. Frame by frame analysis of the volume relations of a ventriculogram related to time, shows close similarity between the derived curves and the scw of the ACG, both in the normal and the diseased patient.⁵⁰ There is a clear distinction, however. While the ventriculogram will localize the exact anatomic portion of the left ventricle, that is dyskinetic, such localization is, of course, not

possible with the ACG. As previously indicated, abnormal scw's were seen regardless of the location of the infarction and even when myocardial ischemia was present. Perhaps the paradoxical bulge seen in the scw is merely the late transmission of the impulse generated by the abnormally contracting myocardium.

More important than the ability of the ACG to reflect left ventricular dysfunction is its apparent enhanced sensitivity over the resting ECG.⁴⁴⁻⁴⁸ Such sensitivity will be of extreme usefulness in patients with progressive symptoms when one cannot perform an exercise ECG. Additionally, the fact that the changes noted in the ACG in patients with acute myocardial infarction, pre-infarction angina, and angina pectoris seem to coincide with the clinical events makes this testing procedure especially attractive, particularly since it can be performed serially and as often as necessary without discomfort to the patient.

It is hoped, therefore, that the ACG will be performed more routinely in patients suspected of having IHD or pre-infarction symptoms when routine tests are non-diagnostic. Whether recorded as a single tracing, and especially when recorded serially, it will provide functional and hemodynamic information that is not possible to obtain from an ordinary ECG. More frequent use of apexcardiography should allow earlier identification of IHD, permit earlier and more rational institution of prophylactic treatment and so help reduce the present high morbidity and mortality from this illness.

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Medical Progress

Platelet Disorders

A Review of Disturbances in Adhesion, Aggregation, and Release Reaction

MERVYN A. SAHUD, M.D., *San Francisco*

WITHIN THE LAST DECADE great progress has been made in our knowledge of the basic cellular mechanisms of blood platelets. The advances helped to clarify the role of platelets in the formation of the hemostatic plug. The tools of investigation readily available to persons interested in the behavior of leukocytes and red blood cells have now been applied to the study of platelets. In addition, new methods, such as aggregometry,¹ platelet factor 3 availability,² and kinetic studies of adenosine diphosphate (ADP) and adenosine triphosphate (ATP) release³⁻⁵ have been developed specifically for platelets. A description of all currently used techniques in the study of blood platelets is beyond the limits of this review, but a list of methods with appropriate references is provided in the Appendix.

Platelet Role in Primary Hemostasis: Current Concepts

Normally, platelets circulate freely (partially because of their negative surface potential⁶) in disc form and are carried along separately and are not attracted to the endothelium. After injury of a blood vessel, platelets immediately adhere to exposed collagen^{7,8} and other subendothelial fi-

bers.^{9,10} Adhesion causes the platelet to swell, changing its shape to a sphere. Approximately 30 to 60 seconds later, adhered platelets rapidly release a large quantity of ADP (and ATP), which results in rapid cohesion of additional platelets. The released ADP can cause release of ADP by other loosely associated platelets.¹¹ The size of this initial loosely held together mass is most likely related to the number of platelets, to the fluid dynamics at the site of injury, to the amount of ADP released, and to the amount of ADP simultaneously degraded to adenosine monophosphate (AMP) and inosine monophosphate (IMP) by plasma.¹² The specific factors required for platelet aggregation include the following: rapid multiple collisions and the presence of fibrinogen, calcium ions, and ADP. Intrinsic clotting is activated by the effect of ADP on initiation of platelet factor 3 availability and the simultaneous collagen activation of contact factors¹³ with the resultant formation of small amounts of thrombin. Thrombin can then induce more platelet clumping as well as render the primary platelet plug impermeable by sealing it with a fibrin mesh. This subject has received critical review.¹⁴

Classification of Platelet Disorders Based on Morphologic Criteria

The newly developed techniques for study of platelets have been used to study some of the classic bleeding disorders as well as new ones.

From the Medical Services, San Francisco General Hospital, and the Department of Medicine, University of California, San Francisco, School of Medicine.

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Reprint requests to: M. A. Sahud, M.D., Medical Services, San Francisco General Hospital, 1001 Potrero Avenue, San Francisco, Ca. 94110.

The term *thrombocytopathia*,¹⁵ used previously to describe a bleeding disorder with a disturbance in platelet factor 3 activity, must now be defined more broadly if it is to continue to serve. This is because many of the so-called thrombocytopathias have now been shown to have impaired platelet aggregation in response to ADP and collagen in addition to impaired platelet factor 3 availability. As will be discussed later, disturbances in platelet aggregation exist with or without impaired platelet factor 3 activity; however, an isolated defect in platelet factor 3 availability is unusual when all platelet function tests are employed.

It is difficult to bring order to the classification of platelet disorders because of the confusion in terms, the extensive variety of laboratory methods employed to characterize these disturbances in the past, and the progressive obsolescence of the existent classification resulting from the rapid expansion of the field. The terms *athrombia* and *thrombocytoasthenia* offer no advantages and should be discarded. In addition, recent demonstration of a relationship between size and function of platelets in the normal state¹⁶ (young large platelets aggregate more strongly in response to ADP¹⁷ and adhere more quickly to collagen¹⁸ than old small platelets) provides a useful classificatory criterion for the discussion of platelet disorders. For this reason, platelet disorders will be reviewed according to their association with microthrombocytes, euthrombocytes, and macrothrombocytes (Table 1). Within each class disorders are divided into *inherited* and *acquired* and are presented in order of frequency.

A bleeding disorder is considered associated with microthrombocytes if the percentage of large forms (megathrombocytes, more than 2.5 μ in diameter) is significantly less than the normal percentage of large forms.* In some instances, assessment of volume-density distribution revealed a preponderance of light small platelets consistent with a reduction in the number of large forms. Similarly, conditions in which the percentage of large forms is significantly greater than the normal percentage are classified as associated with macrothrombocytes. All other conditions are considered in the euthrombocyte group, including a few disorders in which platelet size has not been studied.

*Percentage of large forms (more than 2.5 μ in diameter) in normal subjects ranges from 8 to 14 percent (N=37) (personal observations).

TABLE 1.—Classification of Platelet Disorders Based on Morphologic Criteria

I. Disorders associated with microthrombocytes (proportion of large forms less than 8 percent)
A. Inherited disorders
1) Familial adenosine diphosphate release dysfunction
2) Wiskott-Aldrich syndrome
3) Hereditary hypogranular thrombopathic thrombocytopenia
B. Acquired disorders
1) Uremia
2) Platelet defects in refractory anemia in pre-leukemic state
II. Disorders associated with euthrombocytes (proportion of large forms 8 to 14 percent)
A. Inherited disorders
1) Essential thrombasthenia
(a) Resulting from enzymopathy
(b) Resulting qualitative disturbance of membrane and membrane-bound thrombasthenia with decrease in platelet function
2) Familial adenosine diphosphate release dysfunction
3) Albinism associated with adenosine diphosphate release dysfunction
4) Congenital afibrinogenemia
5) Glycogen storage disease
6) Mongolism (trisomy 21)
B. Acquired disorders
1) Drug-induced platelet dysfunction
2) Cirrhosis
3) Nonfamilial adenosine diphosphate release dysfunction
4) Essential thrombocythemia
5) Polycythemia vera
6) Macroglobulinemia
III. Disorders associated with macrothrombocytes (proportion of large forms greater than 14 percent)
A. Inherited disorders
1) Macrothrombopathia
2) May-Hegglin anomaly
3) Heritable disorders of connective tissue
4) Gray platelet syndrome

Symptomatology of Bleeding Disorders Owing to Platelet Dysfunction

In general, the clinical manifestations of an intrinsic platelet defect are usually skin purpura after minor trauma, dependent petechiae, and mucocutaneous bleeding. In addition, epistaxis, rectal bleeding, and unexplained hematuria sometimes occur. Hemarthrosis is distinctly unusual even in the most severe disorder, essential thrombasthenia. The bleeding tendency varies from time to time in each patient and there may be symptom-free periods. Abnormal bleeding during and after surgical operation is unpredictable.

Disturbances in the platelet number (for example, in essential thrombocytosis or thrombocytopenia) may also occur in addition to intrinsic defects. In patients with thrombocytopenia, spontaneous bleeding usually does not occur until the platelet count falls below 30,000 per cu mm even though impairment of clot retraction often occurs at the 100,000 per cu mm level. When bleeding does occur with platelet counts between 50,000 and 100,000 per cu mm, excluding a surgical lesion, a qualitative defect in the platelet is probably present. Drugs that interfere with platelet function, such as aspirin, should always be avoided since there are adequate substitutes available.^{19,20} In the inherited conditions platelet transfusions have been temporarily used to arrest bleeding and to prevent bleeding during surgical operation. In the acquired disorder, platelet transfusions are not effective since the underlying condition must be treated.

Disorders Associated with Microthrombocytes*

Inherited Disorders

Familial ADP release dysfunction. This mild familial bleeding disorder is characterized by the presence of small platelets, a prolonged bleeding time (or profound prolongation of the bleeding time after aspirin ingestion), normal or impaired platelet factor 3 availability, normal whole blood clot retraction, and defective platelet aggregation in response to collagen suspension, epinephrine, low molar ADP, and dilute thrombin.²¹⁻²⁴ The mode of inheritance is not clear, but appears to be autosomal-recessive in two families^{21,22} and autosomal-dominant in one. The incidence of this disorder has not been determined as yet. The aggregation studies were carried out at 37°C in citrated platelet-rich plasma (CPRP). Aggregation does not occur in response to collagen unless the concentration used is much higher than that used to evoke a normal response in control CPRP. The first wave of epinephrine-induced aggregation is normal or blunted and the second wave is absent. Rapid disaggregation occurs after addition of low molar ADP to the test system. Platelet adhesion to collagen fibrils, measured by phase microscopy, is normal but adhesiveness, measured by the glass bead method, is abnormal. The percentage of large forms is significantly reduced and the

disturbance appears to be caused by a "block" in the release of ADP from the platelet after exposure to collagen and epinephrine. Intraplatelet nucleotide levels are reduced^{21,22} and depletion of the "nonmetabolic" pool of ADP and ATP appears to account for the disturbance.²⁴ Platelet survival studies have not been carried out, as far as is known. Transfusion of platelets temporarily corrects the hemostatic disorder.²²

It is possible that small platelets with reduced ADP levels are manifestations of several different disturbances in intraplatelet structure and function. Ineffective incorporation of inorganic phosphate may result from a disturbance in the platelet membrane or a defect in energy production or utilization. The effect would be a reduction in releasable ADP during induction of the release reaction. A reduction in the ability of the cell to maintain levels of high energy nucleotides may result in loss of cell mass. More investigations are needed to clarify the mechanisms operative in this condition.

Wiskott-Aldrich syndrome. This disorder is transmitted as a sex-linked recessive trait and manifests clinically in infancy with eczema and recurrent infections secondary to deficiencies in both humoral and cellular immune responses. In addition, mild to severe thrombocytopenia exists and about 24 percent of the patients have severe hemorrhagic diathesis not necessarily related to the severity of the thrombocytopenia. Platelets in peripheral blood smears are unusually small with a mean diameter of less than 2 μ .²⁵ Examination of platelets reveals a lack of granulations by light microscopy and a decrease in organelles by electron microscopy.²⁶ A reduction in platelet electrophoretic mobility normally observed after exposure of platelets to collagen and ADP is not observed.²⁶ Platelet adhesiveness and platelet factor 3 availability are impaired. Aggregation in response to ADP, collagen, and epinephrine is decidedly impaired.²⁷ The heterozygous carrier can also be detected by such disturbances in platelet aggregation. A lack of stimulation of intraplatelet citric acid cycle activity after exposure to epinephrine or polystyrene-latex particles is observed in both the homozygous patients and the heterozygous carrier.²⁷ The survival time of autologous platelets is considerably reduced. It is likely that the intracorporeal disturbance causes rapid platelet senescence and sequestra-

*Proportion of large forms less than 8 percent.

tion by the reticuloendothelial system. One of the two patients with this disorder studied in our laboratory does not have the characteristic disturbances in platelet aggregation, but the immunologic deficiency, thrombocytopenia, and microthrombocytes are present. It is likely that several distinct intracorporeal disturbances exist.

Hereditary hypogranular thrombopathic thrombocytopenia. In 1958, a Swiss family with a bleeding disorder characterized by hypogranular platelets and thrombocytopenia was reported.²⁸ The disturbance is transmitted by an autosomally dominant gene and occurs with the allele for blood group O. Ultrastructural studies of the thrombocytes and megakaryocytes of some of these patients show a severe disturbance in dense granules in both platelets and megakaryocytes.²⁹ Platelet factor 3 availability and aggregation with collagen suspensions are defective in these patients. The content of sialic acid in the platelet membrane is low and the number of large platelets is considerably reduced.²⁹

Acquired Disorders

Uremia. Although vascular and plasma factors have been proposed in the past to explain the cause of uremic bleeding, it has become obvious that most of the bleeding abnormalities are related to acquired functional platelet defects. Patients with renal failure and a bleeding tendency usually have prolonged bleeding times, impaired platelet adhesiveness,^{30,31} and defective platelet aggregation *in vitro* in response to ADP, epinephrine, and dilute thrombin;³² however, impaired aggregation in response to collagen is rare (personal observations). Activation of platelet factor 3^{33,34} and prothrombin consumption are impaired in 40 percent of patients. In our studies of 11 patients undergoing chronic hemodialysis the mean platelet size was small (less than 2μ) and the percentage of large forms considerably reduced. This most likely reflects reduction in megakaryocytopoiesis or loss of cell mass owing to the effect of a uremic toxic agent on platelet metabolism. Platelets from uremic patients have normal phospholipid³⁵ and adenine nucleotide concentrations,³⁶ but the concentration and uptake of serotonin are impaired.³⁷ The platelet defect in patients with uremia can be produced in the normal subject by infusion or oral administration of large amounts of urea.³⁸ The defects

in platelet aggregation and platelet factor 3 availability can also be produced *in vitro* by incubating cell-free uremic plasma with normal platelets.³⁹ Furthermore, these platelet defects are reversible by hemodialysis over a period of 12 to 24 hours.

The specific toxic agent responsible for these disturbances in platelet function is still debated, but the most likely agents are urea, guanidin succinic acid,⁴⁰ and phenol and phenolic acids.^{41,42} One group of investigators observed that only guanidin succinic acid is present in uremic plasma in concentrations sufficient to cause an identical platelet disturbance *in vitro*.⁴⁰

Platelet defects in refractory anemia in preleukemic state. A platelet disorder that accompanies the refractory anemia of the preleukemic condition has been observed.^{43,44} In these patients the low grade anemia is associated with leukocytosis, low levels of leukocyte alkaline phosphatase, and elevated platelet counts. The numbers of myeloblasts and promyelocytes in bone marrow are increased. In many respects these patients resemble patients with chronic myelocytic leukemia before blastic crisis. The bone marrow contains numerous nonlobulated megakaryocytes and the peripheral blood contains only small-sized platelets. Platelet aggregation is defective and the incorporation of ¹⁴C-adenosine is impaired. Platelet survival is decreased.⁴⁴

*Disorders Associated with Euthrombocytes**

Inherited Disorders

Essential thrombasthenia. This familial autosomal-recessive bleeding disorder is characterized by a normal platelet count, prolonged bleeding time, decreased or absent clot retraction, and complete absence of platelet aggregation in response to ADP, measured by aggregometer.⁴⁵⁻⁴⁷ More than 100 cases have been reported.⁴⁷⁻⁴⁹ The carrier state may be associated with impaired clot retraction,⁵⁰ although results of other tests of platelet function are within normal limits. On the peripheral blood smear the platelets appear isolated and do not spread normally on a glass slide. Addition of ADP to CPRP results in an occasional small clump of platelets not sufficient to be recorded as a change in optical density by the aggregometer. The platelets adhere normally to

*Proportion of large forms 8 to 14 percent.

subendothelial connective tissue. The nucleotide and 5-hydroxytryptamine concentrations in platelets are within normal limits. Platelet factors 3 and 4 availability is impaired.⁴⁶ Platelet aggregation can be induced only by bovine fibrinogen or antiplatelet antisera.⁴⁶ Release of nucleotides, serotonin, and acid phosphatase is impaired in response to ADP and epinephrine but is normal in response to collagen and thrombin.⁵¹ In contrast to thrombasthenia, only trace amounts of nucleotides and serotonin are released after collagen or thrombin in primary ADP release dysfunction. The life span of autologous platelets in thrombasthenia is normal.

Several investigators have reported disturbances in carbohydrate metabolism with decreased levels of ATP. In addition to a deficiency of glyceraldehyde-3-phosphate dehydrogenase and pyruvate kinase,⁵² a defect in glutathione reductase has been observed.⁵³ Other investigators have found a decrease in platelet fibrinogen without a disturbance in metabolism.^{8,54} A recent hypothesis is that the interaction of fibrinogen with platelet surface thrombasthenin might be impaired.⁵¹ The only effective therapy appears to be transfusion of platelet concentrates or PRP; this was employed successfully in the delivery of a healthy baby from a thrombasthenic mother.⁵⁵

Familial ADP release dysfunction. A family with three affected members with a platelet defect similar to that described for the disorder associated with microthrombocytes but transmitted as autosomal-dominant with variable transmission through two generations has been reported.⁵⁶ However, in these patients platelet adhesion to collagen fibrils is impaired. This platelet disturbance is distinguished from that induced by aspirin by a more rapid disaggregation after addition of low molar ADP to CPRP, with reduced platelet adhesiveness, and a frequently prolonged bleeding time. In addition, the first wave of epinephrine-induced aggregation is blunted. Aspirin does not cause any of these disturbances in aggregation.⁵⁷

Clinically, manifestations include excessive bruising, petechiae, unexplained hematuria, and epistaxis. In some instances platelet transfusions have been helpful during bleeding episodes. It is impossible to predict if hemorrhagic complications will occur during surgical operation.

Albinism associated with ADP release dysfunction. A possible association between albinism and a bleeding disorder has been reported many times.^{58,59} In 1967, 13 patients with a hemorrhagic diathesis characterized by normal platelet count, prolonged bleeding time, and defective platelet aggregation after addition of collagen to PRP were reported. Two patients were unrelated women with albinism. In a third patient with total albinism and a mild bleeding disorder, platelet aggregation was impaired after addition of not only collagen but also epinephrine and dilute thrombin.⁶⁰ The platelet disturbance appears to be a block in the release of ADP similar to that in other recently described platelet functional disorders.²⁴⁻²⁷ In some instances intracellular concentrations of ADP and ATP were subnormal.

Congenital afibrinogenemia. This is a rare disorder transmitted by an autosomal recessive gene. Just over 20 cases have been reported.^{60a} Patients with congenital absence of fibrinogen usually have a prolonged bleeding time and decreased glass bead adhesiveness.⁶¹⁻⁶³ Since washed platelets aggregated poorly *in vitro* when fibrinogen is not added,⁶⁴ it is not surprising that platelet aggregation in these patients is impaired. Specifically, the defect occurs in response to low molar ADP, epinephrine, and collagen but only in CPRP; higher strengths of ADP and collagen induce normal aggregation. No platelet aggregation disturbance is present *in vitro* when heparinized PRP is used.^{65,66} The reason for this discrepancy is unclear. Impaired release of ADP has been observed in response to kaolin and epinephrine but not to connective tissue or thrombin.⁶⁶ The distribution of platelet size and the nucleotide concentration appear unaffected.

Plasma transfusions correct the abnormal bleeding time and platelet adhesiveness. Addition of 10 to 20 mg per 100 ml of fibrinogen to CPRP *in vitro* corrects most of the platelet aggregation defects.⁶⁶ Since the platelets adhere normally to subendothelial collagen the exact way in which fibrinogen aids in the arrest of bleeding remains unknown. More than likely it is responsible for bridging one platelet to another during the aggregation phenomenon.

Glycogen storage disease. A bleeding tendency has been reported in patients with hepatomegalic forms of glycogen storage disease Types I, III, and VI.⁶⁷ Prolonged bleeding time, de-

creased platelet adhesiveness, and impaired platelet factor 3 availability have been observed in Type I of the disease.^{68,69} The defect is believed to be related to the large excess of stored glycogen in the platelets. Adequate studies have not been carried out in Types III and VI. Platelet aggregation and nucleotide concentration and release have not been studied.

Mongolism (trisomy 21). In this disorder the platelet concentration of serotonin is low and the uptake of serotonin is impaired.^{70,71} Platelet function defects may be present but sufficient data have not been obtained.

Acquired Disorders

Drug-induced platelet dysfunction. Although more than 50 drugs have been reported to alter platelet function⁷² only the most widely studied compound, acetylsalicylic acid, will be discussed.

It has been known for many years that ingestion of aspirin aggravates bleeding, and patients with hemophilia have avoided this drug when possible. Several investigators have shown that aspirin ingestion prolongs the bleeding time.⁷³⁻⁷⁶ Quick⁷⁷ popularized this finding and has been justifiably critical of the indiscriminate use of this drug in patients with a bleeding or clotting disorder. Aspirin affects platelet function by inhibiting the release of ADP⁷⁸ from platelets exposed to release inducers, such as epinephrine,⁷⁹ ADP¹¹ and dilute collagen,⁷⁵ but it does not inhibit release of ADP induced by concentrated collagen suspensions or thrombin. The second wave of epinephrine-induced platelet aggregation is blocked.⁷⁹ Ingestion of as little as 150 mg of aspirin can produce these effects, which can last for four to seven days even though the half-life of intravenously administered aspirin is 13 to 19 minutes.⁸⁰ Aspirin has no demonstrable effect on platelet nucleotide levels, surface charge, or rate of ADP conversion in plasma.⁷⁵ High concentrations of aspirin inhibit uptake of glucose⁸¹ and ascorbic acid⁸² and production of lactate.⁸¹ It has been suggested⁸³ that aspirin interferes with early reactions in the biosynthesis of nicotinic acid adenine dinucleotide in platelets. Aspirin also blocks degradation of radioactive ATP to IMP after previous incubation and incorporation of inorganic ³²P into platelets.⁸⁴ This block in ATP degradation may indicate interference with the energy necessary for the release reaction.²⁴

Sodium salicylate does not affect platelet function or prolong the bleeding time.⁷⁵ However, acetic anhydride, another acetylating agent, produces a defect identical to that produced by aspirin: 1-¹⁴C-acetylsalicylic acid effects acetylation of human platelet membranes and granules.⁸⁵ It is most probable that the acetyl radical is the active moiety producing all the platelet defects.

Initially the investigatory emphasis was on the potentiation of bleeding states by aspirin; this problem is solved by avoidance of the drug. The investigation of the antithrombotic potential of agents that induce a mild platelet defect and may thereby inhibit the genesis or propagation of arterial and venous thrombi is more important and urgent.

Cirrhosis. The hemorrhagic tendency in patients with cirrhosis of the liver may be aggravated by thrombocytopenia, low procoagulant levels, abnormal elevation of fibrin-split products, and defective fibrin polymerization. Platelet adhesiveness is elevated⁸⁶ in some patients and reduced in others.⁸⁷ Platelet procoagulant activity is defective in a significant number of patients, but this does not appear related to clinical bleeding. In one study, adenosine diphosphate-induced and thrombin-induced platelet aggregation was impaired in 9 of 20 patients with cirrhosis.⁸⁸ However, the platelet defect was observed only in association with a prolonged thrombin time,⁸⁸ which is consistent with accelerated fibrinolysis and commonly found in advanced liver disease. The increased levels of circulating fibrin-split products not only act as an antithrombin in prolonging the thrombin time, but also interferes with platelet aggregation.⁸⁹

Nonfamilial ADP release dysfunction. This isolated bleeding disorder is characterized by normal platelet count, prolonged bleeding time, decreased platelet adhesiveness to glass, and defective platelet aggregation in response to collagen, epinephrine, and low molar ADP.^{57,90-95} The patients suffer from excessive bruising; the degree of bleeding during surgery is unpredictable. In many respects this disorder is similar to the inherited platelet dysfunction associated with microthrombocytes, although no inheritance pattern has been detected. Levels of all coagulation factors are within normal limits. Clinic-

ally, this disorder is similar to von Willebrand's disease; only platelet aggregation studies differentiate the two.⁹⁶ The distinction between this disorder and that induced by aspirin ingestion is sometimes troublesome.

Essential thrombocythemia. The paradoxical association of a hemorrhagic tendency in patients with a myeloproliferative disorder with increased numbers of platelets has often been attributed to a platelet defect. In three patients with this disorder, platelet aggregation in CPRP was absent in response to epinephrine and reduced after addition of ADP.⁹⁷ The platelets showed normal aggregation to collagen. Uptake of ¹⁴C-labeled serotonin was diminished. After intravenous administration of 4 mCi ³²P to a patient, the platelet count dropped from 5 million to 500,000 per cu mm.⁹⁷ Platelet aggregation in response to epinephrine and ADP gradually returned to normal values.⁹⁷ It appears that the platelet disturbance is a reflection of the disease state and not just of the elevated platelet count.

Polycythemia vera. In five of our six patients with polycythemia vera who were untreated, platelet aggregation in response to epinephrine was totally absent (personal observations). The ADP-induced platelet aggregation was defective in only two of the six patients and was not related to the platelet count. The significance of these abnormalities *in vivo* is unclear.

Macroglobulinemia. In this acquired platelet disorder an interaction between the platelet membrane and macroglobulins occurs.⁹⁸ The bleeding disorder is readily corrected by plasmapheresis. Impairment of platelet factor 3 activity, prothrombin consumption, and platelet aggregation *in vitro* is corrected with removal of the macroglobulins by platelet washing.⁹⁸ The physicochemical adsorption of macroglobulins is believed responsible for the platelet dysfunction. When a patient's platelets are incubated with specific rabbit antihuman macroglobulin serum, the platelet defect is abolished. Monomers of macroglobulin do not produce the defect.⁹⁹ Incubation of normal platelets with macroglobulins can induce the platelet dysfunction.⁹⁸ In some cases of multiple myeloma, protein aggregates may form and induce a similar disturbance of platelet function. More than likely the infusion of dextran has similar effects on platelet function.

Disorders Associated with Macrothrombocytes*

Inherited Disorders

Macrothrombopathia. This familial disorder of platelet function associated with large platelets, often the size of lymphocytes, was first described by Bernard and Soulier in 1948.¹⁰⁰ Two dozen subsequent reports have described a similar bleeding disorder with abnormal prothrombin consumption, platelet factor 3 availability, and variable defects in platelet aggregation.¹⁰¹⁻¹⁰⁸ Some patients have moderate thrombocytopenia with a shortened platelet life span. Morphologic abnormalities have been noted in megakaryocytes as well as in the platelets, and correction of the thrombocytopenia by splenectomy is usually unsuccessful. The bleeding tendency appears unrelated to the thrombocytopenia. Hypogranular instead of hypergranular platelets were reported in some cases in which "agglutination" was defective, bleeding time was prolonged, and clot retraction was normal,¹⁰¹ whereas in eight family members with defective prothrombin consumption and prolonged bleeding time the platelets were abnormally large and granular.¹⁰⁸ The mode of inheritance in this family was autosomal-dominant. In a recent investigation employing newer methods, ADP-induced aggregation was impaired as well as platelet factor 3 activity.^{102,104} In addition, in another family platelet adhesiveness was decreased and total phospholipid content was increased although platelet aggregation with ADP and thrombin determined by visual means was normal.¹⁰⁷ The variability in the degree of platelet dysfunction is further emphasized by the results obtained in two other families.^{105,109} In one family with eight affected members in three generations, ADP-induced aggregation was normal in all eight, even though electron microscopic studies revealed a low content of alpha-granules in platelets of two patients.¹⁰⁹ In the other family, considered to have a platelet membrane defect, electrophoretic mobility of patients' platelets was abnormal in response to ADP.¹⁰⁵

Thrombocytopenia associated with large platelets has also been noted in three patients with Alport's syndrome.¹⁰⁶ In these patients, platelet granules were distributed unevenly. Platelet aggregation in response to dilute ADP, collagen and

*Proportion of large forms greater than 14 percent.

epinephrine was impaired, and platelet adhesiveness to glass beads was absent. Kaolin-induced factor 3 availability was diminished. Release of ADP and ATP from platelets in CPRP after exposure to collagen was considerably reduced. Except for the large size of the platelets, ADP release dysfunction in these patients appears to be similar to the platelet ADP release dysfunction classified under euthrombocytes. Furthermore, the ATP content in the platelets dropped quickly during incubation at 37°C, indicating possible impairment of glycolysis.

May-Hegglin anomaly. This is a familial disorder characterized by appearance of leukocyte inclusion bodies (Döhle bodies) and giant platelets on the peripheral blood smear.^{110,111} Because the patients are often asymptomatic, the condition may go unnoticed. Thrombocytopenia is present in some patients. In many instances the morphologic disturbance of the platelets is not associated with abnormalities in function.¹¹² Platelet factor 3 availability is moderately impaired, and bleeding time and platelet adhesiveness and aggregation are normal.¹¹³

In one family with this disorder no hemorrhagic abnormalities were present despite the mild thrombocytopenia.¹¹² When Hegglin's original patient was restudied¹¹² using newer methods, platelet aggregation in response to thrombin was impaired, platelet factor 3 activity was abnormal, and clot retraction was poor.

Heritable disorders of connective tissue. A spectrum of platelet and coagulation disorders was studied in 31 families with heritable disorders of connective tissue.¹¹⁴ Large platelets were common in most of the patients, but defects in platelet aggregation were inconsistent; defects were present in two of 16 patients with osteogenesis imperfecta, in two of three patients with Ehlers-Danlos disease, in two of five patients with Hurler's disease, and in two of eight patients with Marfan's syndrome. Whole blood clot retraction is sometimes impaired, particularly in patients with Marfan's syndrome.

Gray platelet syndrome. In the only case reported,¹¹⁵ an 11-year-old boy with recurrent petechial rashes, pronounced bruising and variable degrees of thrombocytopenia, the platelets were large and "of a peculiar gray color." Almost all of the platelets lacked granules and the mega-

karyocytes also lacked granules. Curiously, the bleeding tendency disappeared after the platelet count rose in response to corticosteroid treatment and splenectomy; however, the morphologic abnormalities persisted. This unusual case underscores the value of careful morphologic observation of platelets in the peripheral blood smear.

Closing Comments

It is now possible to uncover disturbances in platelet aggregation in patients plagued with mucocutaneous bleeding and excessive bruising. These patients had previously been grouped under the heading "pseudohemophilia A" or "bleeding disorder, cause unknown." The incidence of these mild bleeding disorders is probably much higher than was previously appreciated. Patients may at times have a normal bleeding time; however, a profound prolongation of the bleeding time can be observed two hours after aspirin ingestion if a defect exists. **Often, careful examination of the peripheral blood smear will reveal a preponderance of large or small forms.** In rare instances degranulated forms are noted.

Results of standard tests of bleeding such as platelet count, clot retraction, and prothrombin consumption are often within normal limits. However, the ability of the platelets to aggregate in an *in vitro* test system (aggregometry) is often severely disturbed. Also, activation of platelet factor 3 by ADP, collagen or kaolin may be defective.

Most of the platelet disorders described herein have been investigated intensely by these newer methods. A word of caution is advisable. Since a similar defect can be induced by any number of commonly used drugs, it is reasonable to withhold a diagnosis until the constancy of the defect is determined. The disturbance in platelet aggregation must be found on three successive occasions, during which control specimens are also tested, after abstention from all drugs for seven days. If these conditions are met, a diagnosis can be made. The family should then be carefully studied even when there are no symptoms of bleeding.

The detection of platelet function disturbances is likely to increase. Present attempts to define the subcellular mechanism operative in these conditions should provide a more cohesive picture of the entire spectrum of hemostatic disorders.

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APPENDIX

Techniques Used in the Study of Platelets

Platelet size distribution

Particle size plotter (volume) (1)

Micrometric ocular piece (2)

Megakaryocyte reserve and thrombopoietic potential (3,4)

Life span utilizing diisopropylfluorophosphate³² or chromium⁵¹ (5,6)

Cell populations, separation by:

Osmotic resistance (7)

Differential centrifugation in inert medium (8)

Noncontinuous sucrose gradient ultracentrifugation (9)

Aggregation with collagen, adenosine diphosphate, epinephrine, thrombin, antigen-antibody complexes (10,11)

In whole blood (12)

In platelet-rich plasma (10,11,13)

Adhesion

To glass, collagen, and other foreign surfaces (14-18)

Clot retraction

Whole blood (19)

Platelet-rich plasma (20)

Release reaction (21-23)

Nucleotide studies (24)

Direct quantitation (25)

Uptake, localization and release utilizing C¹⁴ labelled compounds, including serotonin (21-24)

Adenosine diphosphate release, storage, degradation in plasma (26)

Column and thin layer chromatography for mapping intracellular nucleotides (27,28)

Release of potassium, calcium, acid phosphatase, β -glucuronidase (22)

Uptake of glucose, ascorbic acid, amino acids (29,30)

Cellular metabolism

Glycolysis (31)

Citric acid cycle, citric acid metabolism (32, 33)

Oxygen consumption (34)

Incorporation of acetate; synthesis of fatty acids (35)

Protein synthesis (9,36)

Platelet thromboplastic activity—so-called platelet factor 3 (37)

Platelet antiheparin activity (38)

Electrophoresis in response to epinephrine, collagen, adenosine diphosphate (39,40)

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Specialty Conference

Gastroduodenal Stress Ulcers

Moderator: JAMES S. CLARKE, M.D.

Discussants: WALTER F. COULSON, M.D., PAUL H. GUTH, M.D.,
ROBERT K. GRAY, M.D., ARTHUR D. SCHWABE, M.D.,
FRANKLIN L. ASHLEY, M.D., AND ULRICH BATZDORF, M.D.

*From the Departments of Surgery, Medicine, Pathology and
Radiology, University of California, Los Angeles*

■ *Gastroduodenal stress ulcers are frequent sources of massive bleeding and present difficult therapeutic problems. Pathologically, they are acute with minimal reactive fibrosis. Etiology appears related to mucosal vascular engorgement due to microvascular adjustments unrelated to total mucosal blood flow, and without disruption of the gastric mucosal barrier to acid diffusion. Selective intra-arterial injection of vasoconstrictor drugs may arrest bleeding from stress ulcers. Prevention of the many predisposing conditions such as shock, sepsis, and pulmonary insufficiency is the best medical treatment. Once bleeding begins, transfusion, iced saline solution lavage, and (later) antacids are indicated. If bleeding persists, vagotomy with pyloroplasty, vagotomy with subtotal gastrectomy, or total gastrectomy may be required to stop it, but there is disagreement concerning the best operation. Stress ulcers are frequent in association with severe burns and in patients with lesions of the central nervous system. Stress ulcers are appearing with rising frequency, the cause is obscure, and the treatment is unsatisfactory.*

DR. CLARKE:* There is great current interest in our topic, a disease that was rarely recognized as recently as ten years ago. Now we see pa-

tients with bleeding or perforation of stress ulcers almost daily. This emergence of stress ulcer as a common entity and one of increasing prevalence has been noted by physicians in a number of centers. Several disciplines are represented in this conference because of their interest in

*James S. Clarke, M.D., Professor of Surgery; and Chief of Staff, Veterans Administration Hospital, Sepulveda, Ca.

Reprint requests to: J. S. Clarke, M.D., Veterans Administration Hospital, Sepulveda, Ca. 91343.

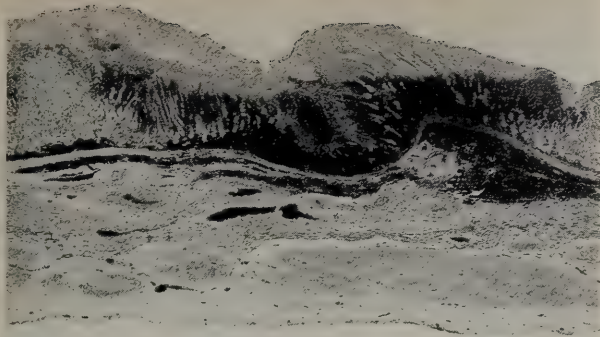


Figure 1.—Early stress lesion virtually limited to gastric mucosa. (Hematoxylin and eosin, $\times 25$.)

various aspects of the stress ulcer problem. The best way to treat chronic duodenal and gastric ulcers has not really been found as yet, and now we have to consider, in a very urgent manner, a whole new area of ulcer disease which, as you will see, is even less settled. We shall start with a discussion of some of the pathological aspects of stress ulceration.

Pathology

DR. COULSON:** The principal feature distinguishing stress ulcers from common peptic ulcer of the stomach or duodenum is acuteness. Stress ulcers occur in either the stomach or duodenum (where occasionally they may involve the second part), or in both. They occur slightly more frequently in the stomach and tend to be multiple. Classically they are small, round, sharply demarcated, relatively shallow lesions, but not infrequently they are more irregularly shaped or even linear. Others may be quite large and go on to penetrate the entire thickness of the gut wall with perforation. The diagnostic feature of stress ulcers is the absence of fibrosis, manifesting their acute nature.

One end of the spectrum may be illustrated by Figure 1, a specimen taken from the stomach of a 28-year-old man who died with extensive amebiasis. He was in a state of chronic hypoxia terminally, and at five and three days before death suffered cardiac arrest. There were multiple gastric ulcers, of which this was one. The lesion is virtually confined to the mucosa, and may therefore be better classified as an erosion than as a frank ulcer. It consists of a localized zone of



Figure 2.—Perforated acute gastric stress ulcer. (Hematoxylin and eosin, $\times 25$.)

coagulative necrosis with associated hemorrhage. The lamina muscularis mucosae remains intact, although hemorrhage extends to the superficial submucosa.

The other end of the spectrum is represented in Figure 2. This was one of multiple ulcers in both stomach and duodenum of a 52-year-old woman who died in uremia complicating bilateral polycystic kidneys. A few days before her death she bled from the gastrointestinal tract and required transfusions. Her stomach was perforated by an acute ulcer that had produced a localized "blow-out" of the wall. The immediate lining consists of necrotic tissue and debris, but the normal strata and particularly the muscle coat extend right to the ulcer margin, with no evidence of fibrosis.

The pathogenesis of these lesions is discussed elsewhere, but of possible interest in this respect is the extent of mucin production by the mucosal epithelium. Figure 3 is a periodic acid-Schiff (PAS) hematoxylin stained section of the mucosa adjacent to a chronic peptic ulcer of the stomach

**Walter F. Coulson, M.D., Professor of Pathology and Chief, Division of Surgical Pathology.

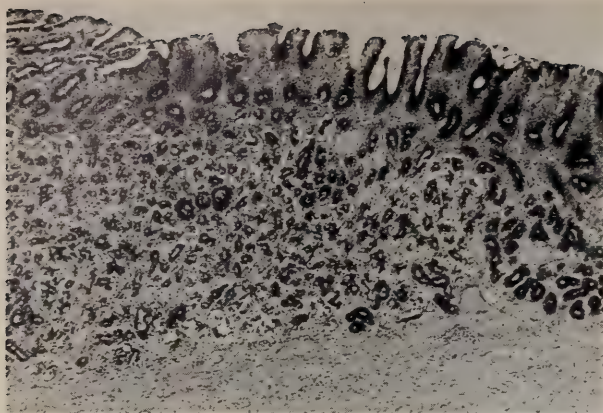


Figure 3.—Mucosa adjacent to a chronic peptic ulcer of stomach, showing epithelial mucin content. (PAS stain, $\times 40$.)



Figure 4.—Mucosa adjacent to lesion depicted in Figure 1, showing dearth of epithelial mucin. (PAS stain, $\times 40$.)

and shows a considerable amount of PAS-positive material. In contrast, Figure 4, taken from the neighborhood of the stress ulcer depicted in Figure 1, shows minimal epithelial mucin.

Pathophysiology

DR. GUTH: * As with the pathogenesis of chronic peptic ulceration, the development of acute stress-induced mucosal lesions can be looked upon as a result of an imbalance between aggressive (hydrochloric acid and pepsin) and defensive (mucus, mucosal cell renewal, barrier to acid diffusion, mucosal blood flow, etc.) factors within the stomach. Under normal conditions there is a balance between the aggressive and defensive factors and no lesions develop. If an imbalance occurs, due either to an increase in aggressive factors (pronounced increase in acid-pepsin secretion) or a decrease in one or more of the defensive factors, then the scale is tipped in favor of lesion formation.

In recent years there have been a number of studies evaluating these various factors in stress-induced lesions. Studies of acid secretion have revealed, with the possible exception of cases of head injuries,¹ no significant alterations in acid secretions in stress situations. This being the case, the problem in stress ulceration must lie within the realm of the defensive factors. As was shown by Dr. Coulson in the human patient with stress ulcers, in experimental situations leading to acute mucosal lesions, such as animals given corticosteroids² or subjected to restraint stress,³

there is a decrease in mucus formation. How this decrease in mucus predisposes to lesion formation is a moot point. The mucus does form a layer over the entire surface of the stomach. This layer probably has a lubricating function but it does not serve as a barrier to the diffusion of acid.⁴ The hydrogen ion is very small and readily passes through the spaces within the mucopolysaccharide molecules making up the mucous layer. Thus the mucous layer does not prevent acid from bathing the surface of the epithelial cells. Another important factor in stress ulceration appears to be mucosal cell renewal. In normal circumstances there is a continual loss of surface epithelial cells from the stomach; these cells, however, are rapidly replaced by proliferating cells coming from the base of the gastric crypts, resulting in an equilibrium between cell loss and cell replacement.⁵ If there is cell damage and increased cell loss, there has to be increased mitotic activity in order to maintain this equilibrium. However, in experimental situations leading to mucosal lesions, such as corticosteroid administration⁶ or restraint stress,⁷ it has been shown that there is a decrease in mitotic activity. There is then inadequate replacement of desquamated cells, and mucosal erosions and ulcerations can develop.

Several years ago, Davenport⁸ developed the concept of disruption of the mucosal barrier to the back diffusion of acid as an important factor in certain experimental gastric mucosal lesions. In normal circumstances there is a barrier to the back diffusion of hydrogen ion and only a relatively small amount of hydrogen ion back-diffuses from the lumen of the stomach into the

*Paul H. Guth, M.D., Associate Professor of Medicine/Gastroenterology; and Wadsworth Veterans Administration Hospital, Los Angeles.

TABLE 1.—Mean Net Flux of Hydrogen Ion in Control and Restrained Rats

Restraining Period	A			B		
	Number of Rats	Number with BD*	Mean H ⁺ Flux (μEq/hr)	Number of Rats	Number with BD*	Mean H ⁺ Flux (μEq/hr)
Control	10	10	-80	9	9	-59
1 hr	10	10	-75	9	9	-47
4 hrs	8	8	-90	7	7	-71
24 hrs	10	10	-77	8	8	-65

*BD: back diffusion.

In calculating net flux of hydrogen ion, acid secreted during the experimental period was accounted for in two ways:

A: H⁺ secreted by similarly treated rats receiving saline instillations instead of acid.

B: Volume distribution of sodium technique (11).

TABLE 2.—Gastric Blood Flow in Restraint Stress

Restraining Period	Cardiac Output (ml/min/kg)	Gastric Flow Fraction (% cardiac output)	Blood Flow (ml/min)			Perfusion (ml/min-g)		
			Antrum	Corpus	Mucosa	Antrum	Corpus	Mucosa
Control	278	0.90	0.06	0.31	0.24	0.56	0.60	0.62
½ hr	281	0.78	0.06	0.26	0.21	0.54	0.49	0.53
4 hrs	336	0.84	0.07	0.36	0.31	0.72*	0.77†	0.80*
24 hrs	422†	0.90	0.09*	0.51†	0.44†	0.99†	0.96†	1.13†

*Significantly different from control at $p < 0.05$

†Significantly different from control at $p < 0.01$

mucosa. Davenport showed that bathing the surface of the stomach with certain agents, such as solutions of acetylsalicylic acid or urea, damages this mucosal (not mucous) barrier. Large amounts of hydrogen ion then penetrate into the mucosa, where a train of pathologic events is begun that leads shortly thereafter to the appearance of gross mucosal lesions. Skillman and Silen⁹ postulated that disruption of the mucosal barrier to acid diffusion may be a factor in stress ulceration. Dr. Donald Gerety, a resident in Gastroenterology at the Wadsworth Veterans Administration Hospital, and I have recently tested this hypothesis in restrained rats.¹⁰ If a rat is immobilized by being wrapped tightly in window screening, and kept so immobilized for four or more hours, it develops mucosal erosions or ulcerations very similar to the type seen in human stress ulcer. Histologic sections reveal that the area of erosion usually involves only the mucosa and does not go through the muscularis mucosa. Probably a better term than stress ulcer would be stress erosion. This is also true, as Dr. Coulson pointed out, of many lesions in the human. At times, though, the lesion does go through the muscularis mucosa and can then be termed a true ulcer. We subjected groups of rats

to various periods of restraint. One hour before the end of restraint we ligated the pylorus of the animals, instilled a hydrochloric acid solution of known hydrogen ion content, and at the end of the restraint period determined the amount of hydrogen ion that had back-diffused. The results are shown in Table 1.

It can be seen that all rats in all groups showed back diffusion (negative net flux). Furthermore, the extent of back diffusion was the same in the control and all restraint groups, in spite of the fact that with increasing duration of restraint there was increasing severity and incidence of stress erosions and ulcers. So, at least in this form of restraint stress, disruption of the mucosal barrier to acid diffusion does not play a role in the pathogenesis of the lesions.

I have also been very interested in the role of mucosal blood flow in stress ulcer. Several years ago we showed that within one-half hour of subjecting rats to restraint stress there is pronounced engorgement of the microvessels in the superficial mucosa.¹² Figure 5A shows a benzidine-stained, cleared section from the stomach of a control rat; the black dots are benzidine-stained red cells and are fairly evenly distributed throughout the mucosa. In rats subjected to

one-half hour restraint there is marked engorgement of the microvessels in the superficial mucosa (Figure 5B). This occurs before ulceration develops, as lesions do not appear until 4 hours of restraint. When lesions develop the erosion occurs through this hyperemic portion of the superficial mucosa (Figure 5C).

We are now studying the dynamics of mucosal blood flow through the mucosa using the ^{86}Rb indicator fractionation technique.¹³ Our results to date are shown in Table 2. With restraint, cardiac output increased at 4 hours and increased even further after 24 hours. However, the fraction or percentage of cardiac output going to the stomach (a little under 1 percent) remained unchanged throughout this period. As the cardiac output increased at 4 hours, so also did blood flow to the antrum, body, and mucosa of the body of the rat's stomach, with even further increase at 24 hours. These increases, however, were strictly in proportion to the increase in cardiac output and hence are related directly to cardiac output and not to any redistribution of blood flow to or within the stomach. Furthermore, it would appear that the mucosal engorgement seen in Figure 5B is not related to mucosal blood flow. The engorgement was present after one-half hour of restraint when mucosal blood flow was normal, and it was present to the same extent after 4 and 24 hours of restraint when mucosal blood flow had increased greatly. Therefore, it would appear that this mucosal engorgement is due to a local microvascular adjustment not related to mucosal blood flow.

It is of considerable interest that in 1956 Doig and Shafar¹⁴ found in the hemorrhagic eroded stomachs of patients dying from cerebrovascular accidents the same type of engorgement of the microvessels in the superficial mucosa. More recently, Bulkley et al¹⁵ demonstrated the same type of superficial mucosal engorgement in rabbits subjected to hemorrhagic shock who developed erosions of the stomach. The hypothesis we are now working on is that a variety of stresses can cause local mucosal microvascular adjustments, unrelated to blood flow, which result in pronounced engorgement of the blood vessels in the superficial mucosa. This engorgement reduces the ability of the mucosa to withstand acid peptic digestion, and peptic ulceration or erosion then develops.

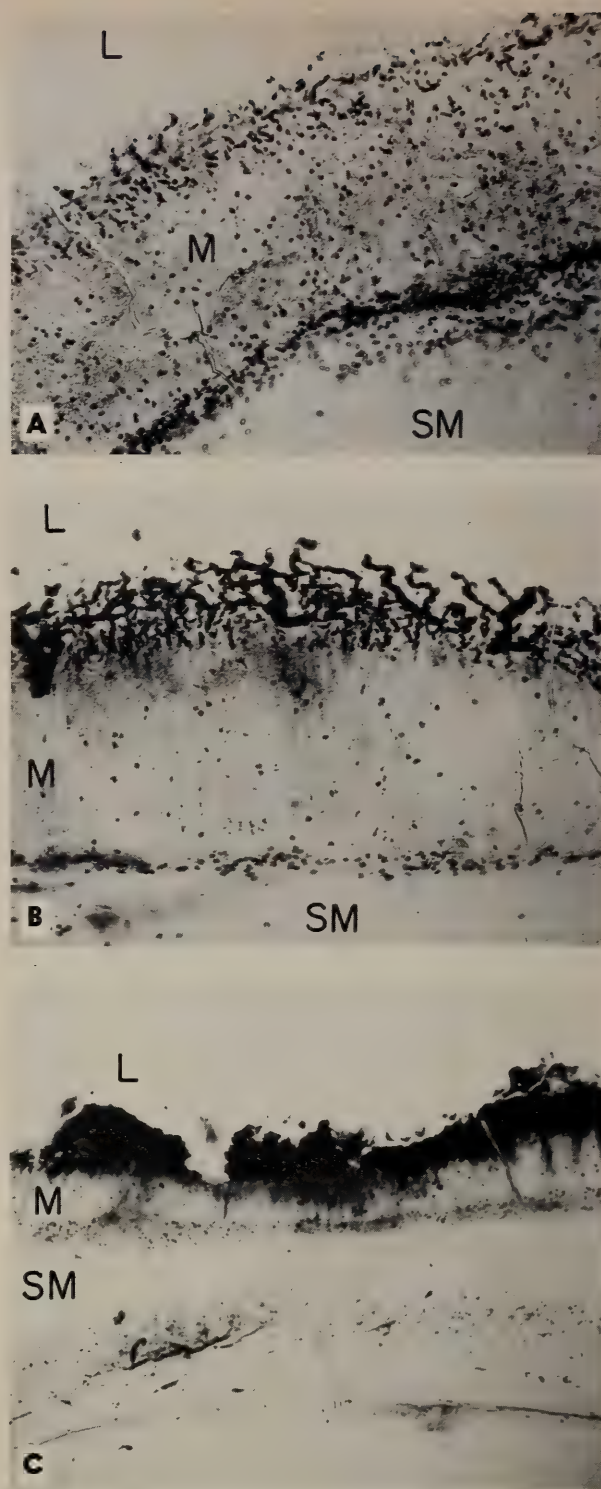


Figure 5.—Photomicrographs of cleared, hemoglobin-stained sections from stomachs of control and restrained rats; L, lumen; M, mucosa; SM, submucosa. (A) Control rat: the small, round, black spots are benzidine-stained erythrocytes; the red blood cells are fairly uniformly distributed throughout the mucosa; $\times 100$. (B) Rat restrained for 18 hours: note the accumulation of benzidine-stained erythrocytes within the microvessels in the area immediately beneath the surface epithelium; $\times 100$. (C) Stress erosion: the erosion primarily involves the hyperemic region of the mucosa adjacent to the lumen ($\times 40$).

Angiography and Intra-Arterial Drugs

DR. GRAY: * Angiography has won increasing acceptance as a valuable aid to the diagnosis of gastrointestinal bleeding during the past few years. This is particularly true of stress ulcers, which are frequently too shallow to be seen on barium studies and would be beyond the reach of the gastroscope if present in the duodenum.¹⁶ An important consideration is that bleeding rates of 0.5 ml per minute or greater are necessary for angiographic demonstration of the bleeding point.¹⁷

Since patients with stress ulcers are frequently not optimal surgical candidates, alternative methods of treatment have been searched for. Once the site of bleeding has been demonstrated, selective arterial infusions of vasoconstricting drugs have recently been used in several centers to control the acute bleeding. The working hypothesis is that vasoconstriction of the infused vessel, with its correspondingly reduced blood flow, will increase the likelihood of stable clot formation at the bleeding point. Considerable experience has been gained by the group at the University of Pennsylvania^{18,19} in the use of pitressin for the treatment of esophageal varices, due to its action in lowering portal venous pressure. The same group has also used pitressin in the treatment of arterial bleeding,²⁰ while at UCLA and the University of Oregon epinephrine has primarily been used^{21,22} (Figure 6). A high success rate has been demonstrated with both drugs and future experience may tell us which is to be preferred.

In angiographic studies, both vasopressin and epinephrine have a vasoconstrictive effect on branches of the celiac axis, with the effect most marked on the splenic, left gastric, and gastroduodenal branches, and somewhat less marked on the hepatic artery.²³ We have studied the effects of pitressin, propranolol, and epinephrine on the superior mesenteric arteries of dogs, using an electromagnetic flowmeter.^{22,24} Because of the inconsistent effect of epinephrine on the superior mesenteric artery, this agent was preceded by the infusion of propranolol, a beta adrenergic blocker. Both pitressin and the combination of epinephrine and propranolol resulted in a rapid decrease in superior mesenteric artery flow to 20 to 30 percent of pre-infusion levels. Following the cessation of the epinephrine infusion,

there was an immediate increase in flow to between 110 and 145 percent of the pre-infusion level. Following the pitressin infusion, however, flow increased slowly and did not reach baseline levels for 15 to 40 minutes. The overshoot following the cessation of the epinephrine infusion indicates at least a theoretical advantage in using pitressin. Epinephrine constricts the portal vein and results in increased portal pressure, while pitressin results in decreased portal pressure. Ischemic bowel changes were not seen with either drug, even after prolonged infusions.

In most cases of bleeding stress ulcers, injection into the celiac axis will demonstrate the site of bleeding. Ulcers in the second and third portions of the duodenum may be demonstrated more effectively by superior mesenteric artery injection. If the rate of bleeding is slow, then a selective injection into the gastroduodenal or left gastric artery may be necessary. Just as a superselective injection is most effective in localizing the bleeding site, a superselective position of the catheter is most effective in delivering the greatest concentration of vasoconstricting agent to the bleeding site. If the small vessels cannot be catheterized, a celiac infusion may be effective. Bleeding from a larger artery, however, may not be controlled by a celiac infusion of pitressin, since the action of the latter is primarily on the more peripheral vessels.²⁰ A diffuse, relatively slow mucosal bleed may be difficult to demonstrate angiographically. A trial infusion of vasoconstrictors into the celiac artery may still be attempted, however, if the clinical evidence of gastric bleeding is strong. Cases where treatment has been unsuccessful have generally been those involving a clotting disorder or where the vessels have not reacted, secondary to arteriosclerosis.²²

The dosage of epinephrine given is usually around 10 mcg per minute, depending on the size of the vessel and the rate of bleeding. The length of infusion has generally been limited to 30 minutes. The initial dosage of pitressin is 0.2 units per minute. The effects of the drug can be ascertained by repeating the angiogram after a 10 to 15 minute infusion and the dosage can be adjusted accordingly. In patients with portal hypertension, pitressin has been infused for a week without complication.²⁰ At the dosages used, systemic effects have been minimal. The cardiac and renal status of the patients treated must be

*Robert K. Gray, M.D., Assistant Professor of Radiology.

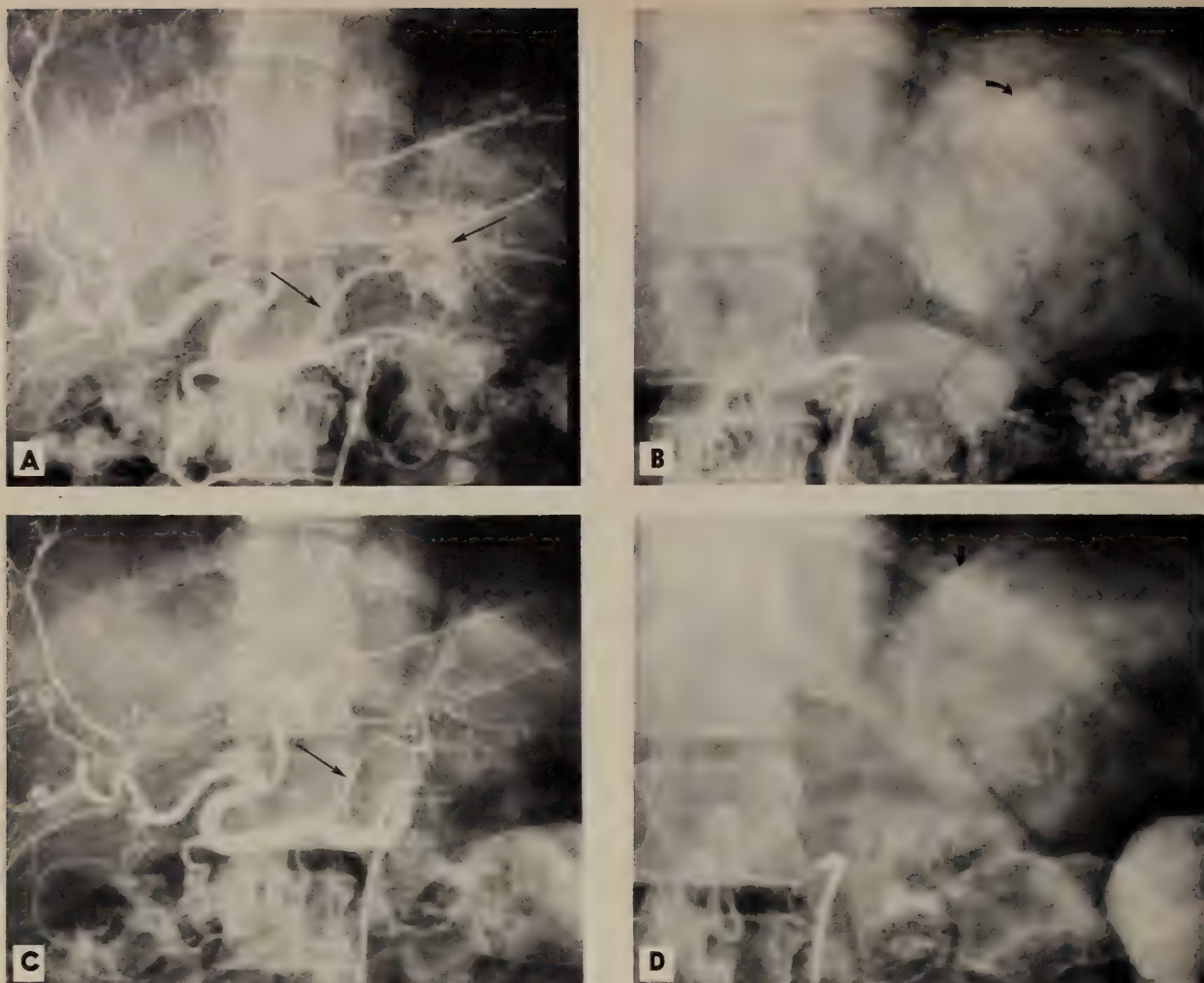


Figure 6.—X-ray studies in the case of a 40-year-old woman with a diagnosis of pseudoxanthoma elasticum, before partial gastrectomy and recurrent bleeding. (A) Arterial phase before administration of epinephrine reveals an angiomatous malformation in the gastric remnant supplied by the left gastric artery. (B) Capillary phase; there is extravasation of contrast in the gastric fundus (arrow). (C) Immediately after the infusion of epinephrine (10 mcg per minute for 4 minutes), there is constriction of all perfused celiac branches, including the left gastric (arrow); the angioma no longer fills; the non-perfused left phrenic artery now fills by reflux. (D) Capillary phase; extravasation is no longer demonstrated; contrast staining is seen in the diaphragm (arrow).

evaluated prior to infusion and must be carefully monitored during the infusion.

The extent of the role of vasoconstrictors in the treatment of gastrointestinal bleeding will not be definitely known until greater clinical experience is accumulated. The results so far have been very encouraging and it is hoped that this method may be used to prepare patients for non-emergency surgical intervention and, in some cases, as the definitive treatment.

Diagnosis and Medical Management

DR. SCHWABE: * Before discussing the diagnosis

*Arthur D. Schwabe, M.D., Associate Professor of Medicine/Gastroenterology, and Chief, Division of Gastroenterology.

and management of stress ulcers, I would like to reemphasize that these lesions occur in association with a variety of clinical disorders (Table 3) and pathophysiologic changes. Neurogenic, vascular, metabolic, and humoral mechanisms, singly or in combination, seem to be related to the development of stress ulceration. More specifically, alterations in mucous production, in splanchnic blood flow, in the secretion of adrenocortical hormones, and in intracellular metabolism have been incriminated.

Diagnosis

The term "stress ulcer syndrome," suggested

TABLE 3.—Conditions Associated with the Development of Stress Ulcers

Trauma
Burns
Fractures
Battle injuries
Sepsis
Septicemia
Pneumonia
Meningitis
Disorders of the central nervous system
Tumors
Cerebro-vascular accidents
Hypertensive encephalopathy
Bulbar poliomyelitis
Hydrocephalus
Miscellaneous
Respiratory failure
Acute myocardial infarction
Major surgery
Hepatic failure
Shock

by Hinchey and associates,²⁵ embraces the complex and variable clinical picture usually observed. The mucosal lesions may appear any time after the stress, regardless of the type, but most commonly between the fourth and ninth days.^{26,27} They have been noted as early as one hour and as late as six weeks after the insult. Stress ulcers occur most commonly in the stomach, frequently in the duodenum, and often in both areas.²⁵⁻²⁹ Occasionally they have also been found in the esophagus and the more distal parts of the small intestine.

Unlike patients with classical peptic ulcers, the vast majority of those who develop stress ulcerations have very few if any symptoms. The first sign is usually an upper gastrointestinal hemorrhage, manifested by hematemesis or melena, or both. In critically burned or injured patients, sudden unexplained clinical deterioration, a falling hematocrit, or hypotension may be the first signal of a bleeding stress ulcer. In some patients anorexia and gastric distension may precede bleeding or perforation. Epigastric pain occurred in less than 5 percent of 103 cases reported by Moncrief, Switzer and Teplitz,²⁶ while bleeding was the first manifestation of stress ulcers in more than 60 percent of these cases. Perforation, however, which has been found in approximately 15 percent of cases in some se-

TABLE 4.—Gastroscopic Findings in Stress Ulceration

Diffuse hemorrhages and erosion
Multiple punctate erosions
Punched-out ulcers
Single
Multiple

ries,^{25,27,29} is usually accompanied by sudden severe abdominal pain followed by the signs expected in "acute abdomen."

The best diagnostic test for a stress ulcer is a high index of suspicion in any acutely stressed patient. Close monitoring of the hemoglobin, hematocrit and stool guaiacs is important for the early detection of bleeding. Supine and upright films of the abdomen are useful in confirming the clinical suspicion of gastric distension and retention, ileus and perforation. The location, type, and extent of gastric lesions may be elucidated by gastroscopy; the gastroscopic abnormalities observed are summarized on Table 4.

These lesions, which are also commonly seen in the gastric fundus, usually have little surrounding reaction or edema.²⁹ Other diagnostic approaches to be considered are upper gastrointestinal x-ray studies and angiography.

Medical Treatment

It is not surprising that the treatment of a disorder of such obscure pathogenesis and associated with a great variety of conditions leaves much to be desired. The best medical treatment is obviously prevention. This may be accomplished by aggressive management of predisposing conditions, particularly shock, sepsis, and pulmonary insufficiency. In severely burned or traumatized patients close monitoring of blood volume, acid-base balance, renal function, and pulmonary ventilation are essential. The patients should be sedated and kept free of pain. Any coagulation defects should be identified and, if possible, corrected promptly. Prophylactic antacids are recommended, although their efficacy in the management of stress ulcers is controversial. Intubation and constant nasogastric suction are recommended for all patients with gastric retention, gastric dilatation, or ileus. This form of treatment will often relieve the nausea and abdominal discomfort, prevent regurgitation and

aspiration of gastric contents, and remove most of the acid that may be secreted.

Once the presence of bleeding from stress ulcerations has been established, blood transfusions are begun. A nasogastric tube is passed into the gastric antrum and, if fresh blood is encountered, the stomach is bathed with iced saline solution. By producing superficial vasoconstriction, this form of gastric cooling may shunt blood away from the mucosa. If bleeding is controlled, the tube is left in place and an antacid drip is begun and continued, along with adequate sedation for at least 72 hours. Thereafter, if normal gastric emptying and good intestinal peristalsis are verified, the tube may be withdrawn and hourly antacids administered. If bleeding continues, however, intravenous pitressin may be used, in order to control the bleeding by reducing splanchnic blood flow. Most investigators agree that surgical therapy is reserved for patients with bleeding stress ulcerations in whom bleeding cannot be controlled by intensive medical therapy.

Surgical Management

DR. CLARKE: As Dr. Schwabe has emphasized, the stress ulcer syndrome occurs in association with a wide variety of stresses. In addition, the pathological picture varies, the lesions being single or multiple, occurring in stomach or duodenum, and ranging from superficial mucosal erosions to deep punched-out ulcers penetrating all layers. They do share the common attribute of acuteness with little surrounding fibrosis, as described by Dr. Coulson. Although the etiology is only partially understood, this too probably is not the same in every instance. From these considerations it follows that no one operation may be best for all cases. Moreover, clinical experiences with operative management must be critically examined as to the underlying stress, pathology of ulceration, timing of operation, and indications for operation. Difficult though it may be to obtain homogeneous and sizable groups of patients for comparison of alternative operative procedures, this will be necessary for valid conclusions.

Stress ulceration with bleeding has a high incidence and carries a high mortality. Palmer³⁰ found that erosive gastritis was the cause of 12 percent of the hemorrhages among 1,400 patients with severe upper gastrointestinal tract bleeding.

Moreover, 9 percent of the patients with this diagnosis died, whereas only 2 percent of patients with bleeding duodenal ulcer and 3 percent of patients with bleeding gastric ulcer died. Katz and Siegel³¹ found acute gastrointestinal mucosal lesions to be the most frequent source of heavy upper gastrointestinal bleeding in a city hospital with a high proportion of cirrhotic patients.

There is a tendency to operate later than usual on a patient with a bleeding stress ulcer because the patient is usually very ill from the associated insult, stress bleeding often stops with nonoperative therapy, and operative control of bleeding is frequently uncertain. At the same time, the patient is in poor shape to withstand the cardiovascular effects of long continuing bleeding; multiple transfusions carry increasing risk, and laparotomy will occasionally uncover intraperitoneal abscesses in need of drainage. On balance, there seems to be no reason to depart from the indications for timing of operation outlined by Nyhus,³² who advised operation if there is need (after initial stabilization) for more than 1,500 ml of whole blood transfusion in any 24-hour period, or if bleeding continues for more than 48 hours from onset, or recurs after initial cessation under hospital management, or is accompanied by perforation. Hinchey and co-workers²⁵ agree that the same rules should govern surgical management of hemorrhage secondary to stress ulcers as of hemorrhage from chronic peptic ulcers. Data are sparse as to the proportion of patients bleeding from stress ulcers that will need operation, but Lucas and associates³³ operated on 38 of 300 patients with major gastric bleeding complicating injury or sepsis.

There is general agreement that simple perforation of stress ulcers should be treated by prompt closure and omental reinforcement.²⁵ Vagotomy and a drainage procedure may be added.²⁷ A large perforation may make closure impossible and require gastrectomy to include the ulcer or to avoid narrowing of the pyloric channel. David, McIlrath and Higgins²⁷ had a mortality of 43 percent for perforating lesions, higher than their 26 percent rate for bleeding ulcers and all their deaths from perforation occurred in cases in which operation was delayed 48 hours or more from onset of symptoms.

The operations proposed for bleeding stress ulcers include subtotal gastrectomy,³⁴ near-total or total gastrectomy,³⁵ vagotomy and pyloro-

plasty with suture ligation of discrete bleeding points,³⁶ and subtotal gastrectomy plus vagotomy.³⁷ The primary rationale for the excisional procedures is that they remove the source of bleeding. A secondary advantageous effect, rarely mentioned by the proponents of resection, may be the removal of gastrin-mediated stimulation to acid and pepsin secretion in the gastric remnant with associated reduction in mucosal blood flow.³⁸

The rationale for vagotomy is that it reduces acid secretion and mucosal blood flow. Although the importance of the acid-pepsin aggressive factor in stress ulcers has been widely minimized, there is both laboratory and clinical evidence supporting its significance. Gottschalk and Menguy³⁹ demonstrated that gastric hydrochloric acid plays an important role in gastric mucosal injury in rats from parenterally administered aspirin. Bulkley, Goldman and Silen⁴⁰ showed in rabbits that intraluminal acidity is required for intraluminal aspirin to cause breakdown of the mucosal barrier to ionic diffusion; it is also required for high transmural pressure to cause hemorrhagic ulcers. Similarly, in human stress ulcers gastric hydrochloric acid may play a permissive role even if not the primary one, and even if not present in unusually high amounts. The reported evidence concerning gastric acid hypersecretion in the stress ulcer syndrome is conflicting,²⁵ but hypersecretion has been documented in some instances of bleeding associated with trauma or sepsis.^{33,41} Gastric acid hypersecretion occurs regularly in comatose patients with head injuries.⁴²

Besides reducing acid secretion, vagotomy reduces gastric mucosal blood flow, possibly from opening submucosal arteriovenous fistulas.^{43,44} This seems to have value in arresting bleeding from superficial erosions,³⁶ but makes less sense when applied to deeper ulcers entering large blood vessels, as was noted by Moody in his discussion of Matsumoto's paper.⁴⁴ Moreover, the vascular effects of vagotomy are temporary, lasting less than half an hour.^{43,44} However, mucosal vascular congestion and hemorrhage do appear to be important initiating events in stress ulcer.^{12,14,33} Vagotomy may have beneficial effects on vascular reactivity, either directly or through inhibition of release of serotonin or histamine.⁴⁵

Comprehensive review of papers on results of operations for stress ulcers is impossible here, as the number is already great and current output

approaches a torrent. A good recent review is that by Hinchey and associates.²⁵ Randomized assignment of patients to operations is lacking and will be difficult to accomplish due to the wide variety of circumstances leading to the final common catastrophe of massive bleeding. Despite the large numbers of patients involved, selection of homogeneous groups for alternative operative procedures must limit the numbers in each category severely, and cooperative studies involving several hospitals will be required to reach any firm conclusions. Criteria of operative success have been early mortality and frequency of continuing or recurrent bleeding. The overwhelming consideration of simple survival in these sick bleeding patients has precluded evaluation of the various operations as to the late effects such as dumping, diarrhea, and nutritional adequacy.

A useful review of the English literature on results of surgical treatment has been published by Drapanas and co-workers.⁴⁵ The patients had massive bleeding from acute gastric mucosal disease. Of 81 patients undergoing subtotal gastrectomy, 52 percent re-bled and 30 percent died. Of ten patients undergoing total gastrectomy none re-bled or died. Thus, re-bleeding is frequent from ulcers in the gastric remnant, where these ulcers often occur.^{28,46} It is unlikely that these perfect results for total gastrectomy can be achieved in the long term, due to the technical difficulty and risks of total gastrectomy itself and the illness of the patients, but the certainty of stopping the bleeding has strong appeal to some.^{35,43} Others have been discouraged with even subtotal gastrectomy due to technical problems such as duodenal stump disruption.²⁸

Vagotomy and gastrectomy seems most widely favored at present.^{37,45,47,48} Among 44 patients, Drapanas and associates⁴⁵ found that only 15 percent re-bled and 20 percent died. It is therefore more effective than subtotal gastrectomy alone in preventing re-bleeding. Although vagotomy and drainage showed a higher incidence of re-bleeding (29 percent of 118 patients), its mortality was about the same (19 percent). Vagotomy, suture ligation of bleeding points, and pyloroplasty constitute a shorter and technically less hazardous operation than resection, but one less certain to control the bleeding. Since the mortality results so far are comparable, many observers prefer the simpler procedure^{33,36,43} un-

der some circumstances. Frequently it is the only feasible operation if there are abdominal adhesions or infection.

Finally, it is unlikely that one operation is best for all stress ulcers. Among factors to be considered are the reversibility of the underlying stress (for example, by drainage of abscesses); history of past ulcer disease, favoring an effective acid reducing procedure; the number, distribution, and depth of the ulcers; the patient's ability to withstand the proposed operation or more than one operation in case of re-bleeding; and the long-term nutritional effects of the contemplated operation. Thoughtful rules for selection of operation were stated by Lucas and co-workers,³³ who advocate vagotomy and pyloroplasty if (a) bleeding stops after vagotomy and (b) there is an initial precipitating factor which is under control or will be within 48 hours; otherwise they prefer subtotal gastrectomy and vagotomy. Olsen, Foley and Simon⁴³ advocate vagotomy and pyloroplasty for hemorrhagic gastritis if the patient's condition is good and the gastritis has a reversible etiology; otherwise they prefer near total gastrectomy. David, McIlrath and Higgins²⁷ are guided by the pathologic findings, favoring vagotomy, suture ligation, and pyloroplasty for a single duodenal ulcer, but partial gastrectomy and vagotomy for multiple lesions. Clearly, our level of uncertainty on this complex subject should discourage heated dogmatism in favor of any single operation.

Burn Stress Ulcers

DR. ASHLEY:* The earliest reports of acute peptic ulceration appeared in 20 A.D., when Celsus observed stress ulcers and gastrointestinal symptoms in men during military campaigns.⁴⁹ In 1842, Curling⁵⁰ reported on 12 cases of duodenal ulceration in burn patients. Several sporadic case reports had appeared in the literature in the 20 years preceding his paper, but Curling established firmly the relationship of stress secondary to burns leading to peptic ulceration. Harvey Cushing⁵¹ published his theories on stress ulceration related to hypothalamic lesions in 1932; these are similar lesions but a different syndrome. In the last decade, the establishment of the Surgical Research Unit at Brooke Army

Hospital under the direction of Dr. John Moncrief has led to more detailed studies and a more penetrating view of the problem.

Definition and Description

An acceptable definition for stress ulcer was suggested by McHardy in 1959⁵²: The lesion "denotes a superficial, relatively noninflammatory mucosal and submucosal erosion of short duration accompanied by minimal symptoms but fraught with potential hemorrhage, perforation and chronicity."

Curling's ulcers have characteristic features that distinguish them from acute or chronic ulceration of the peptic ulcer disease type. They are well circumscribed, sharply demarcated punched-out lesions that show no surrounding or underlying induration or edema, and minimal injection. Most are superficial but they may be deep, leading to penetration and perforation of surrounding structures. Curling's and Cushing's ulcers represent an interesting group of local pathological effects in the upper gastrointestinal tract which *may* have a general pathophysiologic cause.

Incidence

The incidence of Curling's ulcer seemed to rise with the years, but this is attributed to the increased skill in identifying the complications. In a 1964 review, Moncrief, Switzer and Teplitz²⁶ quoted a figure of 25 percent or greater as the probable incidence of ulcer occurring in association with thermal burns; this was based on autopsy data. Actual clinical experience indicated symptomatic ulceration at around 5 percent of burn cases.

Clinical Features

A characteristic clinical picture and course of events have been constructed through the years⁵³⁻⁵⁵ and it is still true today, although until recently the postmortem data have not been as satisfactory. This may be because the pathologist was not looking for stress ulceration in burn patients who died from other causes. The usual time of onset of hemorrhage is the eighth to tenth postburn day. Perforation is likely to occur around the thirtieth day. The Brooke Army Hospital study²⁶ of 103 patients with Curling's ulcer demonstrated that 40 percent had minimal symp-

*Franklin L. Ashley, M.D., Associate Professor of Surgery/Plastic Surgery, Chief, Division of Plastic Surgery. Robert S. Amonic, M.D., collaborated in the preparation of this section.

toms either clinically or as noted at autopsy. In most cases, the first evidence of a lesion was bleeding, and in many of these it was massive exsanguinating hemorrhage with sudden onset and no prodrome. The relationship between extent of burn and frequency of ulceration has not been precisely determined, but there is no question that the majority occurs in patients with significant burns covering 30 to 60 percent of the body surface. Those with greater burns may die before the onset of ulcer complications. Before 1957 it was believed that most lesions were duodenal and were solitary. Moncrief's recent study²⁶ shows a 2-to-1 incidence of gastric over duodenal ulceration and a great preponderance of multiple lesions.

Etiology

No single etiologic concept encompasses all the mechanisms that appear to take part in such ulcer formation. It has not been possible to simplify the etiologic factors, since all acute stress ulcers cannot be attributed to adrenocortical hyperactivity or to simple gastric hypersecretion, or to acute mucosal-vascular changes. These factors are important, but the actual causal relationships remain undetermined. Stress seems to be the central common denominator in the production of acute peptic ulceration. In burn stress ulcers, there are several factors to be considered. First is the finding that hemoconcentration in the wall of the stomach and duodenum is a definite contributor to the production of ulcer; second, ulcers result from either failure or hyperactivity of the adrenal gland.

Experimental evidence by Friesen⁵⁶ in 1950 and Dahl⁵⁷ in 1959 showed conclusively that postburn hemoconcentration is an etiologic factor for Curling's ulcer. They found that ulceration developed only in animals with hemoconcentration and mucosal congestion and was prevented by avoiding these conditions. Stress ulcers have also been experimentally produced by adrenal hypersecretion studies. Following burns there is in dogs an increased contractility of the stomach and duodenum, particularly the pylorus, with chronic contractions of the stomach. In rats, a delayed emptying time is seen. In the cases seen at Brooke²⁶ in the humans, abdominal distension, vomiting and an occasional acute gastric dilatation were seen with surprising frequency. Studies on gastric secretion are

contradictory and confusing, but the volume and degree of acidity varies considerably between animals within the same species, and in humans. There does seem to be a tendency to increased gastric acidity in the human as reflected by increased uropepsin excretion. However, this does not correlate well with chemical findings of ulceration.

Treatment

Treatment is often started late because of the benignity of symptoms and suddenness of onset of gastrointestinal bleeding. Early preventive ulcer therapy has not been demonstrated to be effective. Intubation, or antacid regimen with the addition of an anticholinergic drug reduced the incidence of severe complications, but Moncrief²⁶ reports no significant change in the incidence of bleeding with prophylactic measures.

It is obvious that surgical intervention is mandatory in many cases, especially when massive uncontrollable hemorrhage has occurred. A conservative approach of careful observation and a high index of suspicion is a practical method applicable to all burn patients. Vigorous and intensive medical treatment of a proved lesion is mandatory, and operative intervention should be reserved for massive hemorrhage and perforation. The actual surgical technique should be the simplest to accomplish the job, since the risk of operation is greater than usual and convalescence and wound healing are seriously retarded. Vagotomy and pyloroplasty, or resection with antrectomy and vagotomy, are satisfactory procedures; in some cases, however, more radical gastrectomy is indicated to control hemorrhage from multiple bleeding sites.

Summary

Curling's ulcers appear much more frequently than was previously believed, and are likely to go unrecognized until autopsy or until they make their presence known by hemorrhage or perforation.

Although the early symptoms often go unrecognized, these lesions may cause indigestion or other vague symptoms before hemorrhage or perforation occurs. One should be alert to the early appearance of such symptoms and institute appropriate medical therapy. Surgical treatment should not be delayed once the inevitability of the course becomes obvious.

The Central Nervous System and Stress Ulcers

DR. BATZDORF:* Cushing⁵¹ collected the first series of patients in whom gastrointestinal ulceration and hemorrhage were seen in association with lesions of the central nervous system. Many of his patients had recently undergone operation for intracranial tumors. On the basis of autopsy examinations he postulated a diencephalic lesion as the cause of these ulcers, now often referred to as Cushing's ulcers. Although not common in neurosurgical practice, such ulcers constitute a serious risk to patients and must therefore be recognized and treated effectively. Today we know that Cushing's ulcers are seen most commonly in head injury cases as well as in brain tumor patients, such as described by Cushing. Occasionally they may also be seen in association with cerebrovascular disease. Thus Cushing's ulcers are clearly of concern to neurosurgeons.

One of the difficulties posed in any consideration of Cushing's ulcers is to distinguish between the effects of stress, such as may result from general anesthesia, widespread trauma or fever, and the effects of the structural lesion of the central nervous system. Closer scrutiny of Cushing's original cases only confirms this problem, as many of his patients had high fevers shortly before death. The most distinctive feature of Cushing's ulcers is that they may be associated with hydrochloric acid hypersecretion, a feature not shared by the other stress ulcers discussed here. We also realize that the central nervous system lesions that may be associated with Cushing's ulcers are often difficult to pinpoint, since the destructive effects of both tumors and head injuries are rarely very focal. The neural connections of the hypothalamus are such that lesions in different areas of the brain and, in particular, of the brainstem, could give rise to diencephalic stimulation. In the modern era some of the earliest work was done by Dr. John French (now director of the UCLA Brain Research Institute), working with Dr. Robert Porter, another neurosurgeon. In their own patients and their review of the literature,⁵⁸ they found lesions involving the diencephalon to be the most common ones associated with Cushing's ulcers, followed by cerebellar lesions. Gastric lesions greatly exceeded those of the duodenum. The

esophagus was also commonly involved, either alone or together with stomach or duodenum, and occasional colon lesions were seen. Roughly half of the ulcers they reviewed were hemorrhagic, the remainder being erosive lesions, including such entities as gastritis, gastromalacia, and nonhemorrhagic ulcers.

The pathophysiology of these hypersecreting ulcers is of considerable theoretical interest and has particular relevance to their management. The earlier experimental studies by Porter, Movius and French⁵⁹ pointed to the critical role of the hypothalamus. More recent work has been reviewed extensively by Brooks⁶⁰ and by Emas.⁶¹ Anterior hypothalamic stimuli reach the vagus nerve via the brainstem. Vagal activity may result in acid secretion by two mechanisms, the more physiological gastrin pathway, and as direct vagal stimulation of the parietal cells. The existence of delayed gastric acid stimulation by a hypothalamic-pituitary-adrenal cortical mechanism is doubtful.⁶⁰

We recognize that excessive secretion of hydrochloric acid is only one of the factors contributing to ulcer formation in these patients. Diminished protective mucin, decreased motility resulting in stasis of acid gastric contents, and inadequate perfusion with consequent tissue anoxia may all promote ulcer formation.⁶² These factors are all under autonomic control. In the clinical situation, hypothalamic vagal stimulation may be opposed by sympathetic stimulation in response to stress.

Vagotomy has been considered for patients with Cushing's ulcer and would be effective in controlling hypersecretion but, of course, it would be insufficient treatment for a patient with an actively bleeding ulcer. Two recent papers have focused on the medical management of acid hypersecretion in patients rendered comatose by head injuries: acid hypersecretion was demonstrated in some patients treated without steroids⁴² as well as in patients receiving steroid medication.⁶³ Hyperacidity in both groups of patients responded to tridihexethyl chloride, an anticholinergic agent. The authors of those papers expressed hope that, in the future, high-risk patients may be identified by gastric analysis and treated prophylactically. An interesting observation made by these investigators as well as by earlier workers is the peak incidence of gastro-

*Ulrich Batzdorf, M.D., Assistant Professor of Surgery, Division of Neurology.

intestinal bleeding between the sixth and eighth day after the head injury.

A critical review of the entire question of ulceration and hemorrhage in association with central nervous system lesions is essential before we can be certain that these represent a response uniquely different from other types of stress ulcer.

One last consideration should be mentioned—the differential diagnosis. In the head-injured patient, bleeding from the nasopharynx must be considered in the differential diagnosis of hematemesis. In the postoperative patient, the possibility of acute gastric dilatation should not be overlooked.

Discussion

Question from the Audience: Dr. Schwabe, in view of the statement that vagotomy shunts the blood away from the mucosa, is there any room for atropine in medical therapy?

Dr. Schwabe: There is no evidence that anticholinergics either prevent stress ulcers or facilitate their disappearance. They do, on the other hand, tend to aggravate gastric distension and may produce an ileus. For these reasons, most observers feel that they have no part in the management of these patients.

Question: Dr. Gray, is the upper gastrointestinal series ever of benefit in the diagnosis of stress ulcers?

Dr. Gray: This primarily depends on which tests are available. Arteriography and endoscopy have a better yield in diagnosing stress ulcers. However, if they are not available, then upper gastrointestinal tract studies may help rule out other causes for bleeding and may occasionally demonstrate a stress ulcer.

Question: Dr. Gray, what is the minimum amount of bleeding to be picked up by angiography? For instance, I have a patient who was bleeding between 20 and 30 ml a day; could such a lesion be found angiographically?

Dr. Gray: To visualize the actual point of bleeding, which is determined by extravasation of contrast into the gut, 0.5 ml per minute is needed. However, even if the patient is not actively bleeding, vascular malformations, small bowel tumors, and other lesions that may be causing bleeding may be visualized angiographically where other diagnostic means have failed.

Question: Dr. Batzdorf's comments were of

great interest to me. There seem to be several points of difference with those of previous speakers. For example, the fact that gastric hypersecretion has been demonstrated in patients with cerebral lesions, and that anticholinergics seem to be effective in their management. Does this, then, in the opinion of any of the speakers, justify the separation of the so-called Cushing's ulcer into a separate group of stress ulcer syndrome?

Dr. Batzdorf: I think that should probably be left to the other discussants, since ours are a small number, but I do have the impression that they are a distinct group in the sense that they are hypersecreting ulcers. Perhaps Dr. Schwabe would comment on this.

Dr. Schwabe: As I said at the outset of my presentation, there are many different precipitating events and there are many different causes for stress ulcer. That is why I like the idea of referring to the stress ulcer syndrome, or perhaps syndromes. While acid secretion may range from achlorhydria to hyperchlorhydria, the vast majority of patients have hypochlorhydria. There are throughout the literature instances where patients were found to be hypersecretors, and one can only speculate that their ulcers may be produced by a somewhat different mechanism. In those patients who do have hypersecretion of acid, I would rely on gastric suction initially and hourly antacids thereafter.

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A GAUGE OF ANTIBIOTIC OTOTOXICITY

As a rule of thumb, if an antibiotic is effective only by injection, it can be ototoxic. In other words, most antibiotics that are effective by mouth are not ototoxic to any great extent. . . . Aspirin might be ototoxic by mouth, I suppose, in huge doses over a long period of time—but it's not a permanent loss. If the drug is effective only by injection, it can indeed produce a permanent sensorineural loss.

—HOWARD P. HOUSE, M.D., Los Angeles
 Extracted from *Audio-Digest Otorhinolaryngology*, Vol. 3, No. 6, in the Audio-Digest Foundation's subscription series of tape-recorded programs. For subscription information: 1930 Wilshire Blvd, Suite 700, Los Angeles, Ca. 90057

MEDICAL STAFF CONFERENCE

Immunological Mechanisms of Glomerulonephritis

These discussions are selected from the weekly staff conferences in the Department of Medicine, University of California, San Francisco. Taken from transcriptions, they are prepared by Dr. Sydney E. Salmon and Robert W. Schrier, Assistant Professors of Medicine, under the direction of Dr. Lloyd H. Smith, Jr., Professor of Medicine and Chairman of the Department of Medicine. Requests for reprints should be sent to the Department of Medicine, University of California, San Francisco, San Francisco, Ca. 94122.

DR. SMITH:* In recent years it has become increasingly apparent that a variety of renal disorders may be mediated through immunological mechanisms. This appears to be the case in certain systemic disorders such as lupus erythematosus, as well as in other diseases which conventionally were considered to be limited to the kidney. Today we welcome Dr. Curtis Wilson as our guest at Medical Grand Rounds. Dr. Wilson will discuss the various experimental models of glomerulonephritis which he has studied in conjunction with Dr. Frank Dixon and associates in the Department of Experimental Pathology at Scripps Clinic and Research Foundation.

DR. WILSON:† Thank you, Dr. Smith. Investigations over the past 70 years have led to the identification of two distinct immunopathological mechanisms capable of producing glomerulonephritis. Specific antibodies are common to both mechanisms. In the first, antibodies react with circulating antigens to form circulating immune complexes. These complexes can fix complement and deposit along the glomerular base-

ment membrane (GBM). Since deposition is random, these complexes appear as granular deposits along the GBM when sections are stained with fluoresceinated antibodies specific for either the antibody, the involved antigen, or complement. These deposits can also be identified as electron dense material with the electron microscope in subepithelial, intramembranous and subendothelial positions.¹ The second mechanism comprises so-called anti-GBM antibodies which are specific for antigens present in the GBM and react directly with the GBM, where complement may be fixed. Since such antibodies react all along the GBM, they appear as linear deposits by immunofluorescence. The key to distinguishing the two mechanisms, then, is immunofluorescent study in which frozen sections of kidney tissue are stained with fluorescein-labeled antisera specific for human immunoreactants (Figure 1).

Either variety of glomerular injury probably results from the action of similar immunological mediators. When antibodies react with their specific antigen, GBM-associated or circulating, to form immune complexes, the complement sequence may be activated. The activated trimo-

*Lloyd H. Smith, Jr., M.D., Professor and Chairman, Department of Medicine.

†Curtis B. Wilson, M.D., Department of Experimental Pathology, Scripps Clinic and Research Foundation, La Jolla.

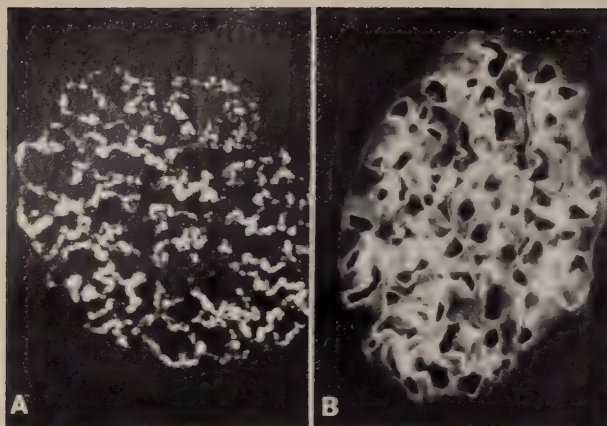


Figure 1.—A. Granular immunofluorescent deposits of bovine serum albumin (BSA) typical of immune complexes are present in a random pattern along the GBM of a rabbit with proteinuric chronic (daily injection) serum sickness. (Stained with fluorescein conjugated rabbit anti-BSA serum, original magnification X250) B. Linear immunofluorescent deposits of duck immunoglobulin typical of anti-GBM antibody are found in a smooth, continuous pattern in a rat glomerulus 4 hours after injection of duck anti-rat GBM antibody. These antibodies apparently gain access to the GBM through endothelial pores. (Stained with fluorescein conjugated rabbit anti-duck gamma globulin serum, original magnification X400)

lecular C5, 6, 7 complex and fragments of C3 and C5 are chemotactic for polymorphonuclear leukocytes (PMN), causing these cells to accumulate at the site of antigen-antibody interaction. PMNs actually displace the endothelial lining of a glomerular capillary to approximate themselves along the GBM in experimental nephritis and in human immune complex nephritis.²

PMNs appear to produce injury largely by release of enzymes and other lysosomal proteins.³ These enzymes are capable of releasing fragments from rabbit GBM *in vitro*, and large fragments of the GBM have been identified in the urine of animals with experimental nephritis. Similarly, human neutrophils contain proteases, collagenase and elastase which could produce injury to the human GBM. Alternate pathways of injury must also be involved, since experimental anti-GBM antibodies from fowl and some mammals can produce experimental glomerular injury without obvious complement or PMN participation. Likewise, approximately one-third of patients with active anti-GBM antibody induced glomerulonephritis do not have detectable glomerular-bound complement by the usual immunofluorescent techniques. The kinin system, coagulation system and other pathways are being investigated to determine whether they may play

a part in the alternative routes of glomerular injury. In view of the common mediation pathways of glomerular injury, it is not surprising that often no distinctive histological lesions have been identified by light microscopy to separate immune complex from anti-GBM antibody glomerulonephritis. Indeed, the immunological mechanism does not appear to govern the histological alteration; rather the histological lesion with the clinical picture it produces seems to relate to the magnitude and speed with which the immunoreactants interact in a given host.

This can best be demonstrated in experimental animals in which the cause of the glomerular injury is clearly defined. Bovine serum albumin (BSA) induced chronic serum nephritis of rabbits⁴ presents a broad histological spectrum. Membranous glomerulonephritis, characterized by capillary wall thickening, and rapidly progressing, proliferative glomerulonephritis are both found in this experimental model. The membranous lesion develops most characteristically in rabbits with a meager immune response secondary to prolonged exposure to a low daily level of circulating immune complexes. In contrast, severe proliferative glomerulonephritis develops rapidly in actively immune rabbits which are given large amounts of antigen to achieve immunological balance.

The most common lesion, however, induced in chronic BSA serum sickness is a combination of the membranous and proliferative features. Histologically, this lesion is difficult to distinguish from the lesion induced by heterologous anti-GBM antibody, although the immunofluorescent differentiation is clear with the typical granular, rather than linear, deposits of immunoglobulin. Immunofluorescent identification of the pattern of immunoreactant deposition is then mandatory to differentiate between the two major immunological pathogenic mechanisms.

Immune Complex Glomerulonephritis

Immune complex mediated glomerulonephritis appears to be responsible for possibly more than 90 percent of human immunological nephritis. Von Pirquet in 1911 recognized the relationship between the host immune response to foreign serum protein and the development of serum sickness. During the 1950's the independent experiments and concepts of Germuth^{5,6} and

I*BSA ELIMINATION-CIRCULATING BSA ANTI-BSA COMPLEXES-DEV. OF LESIONS

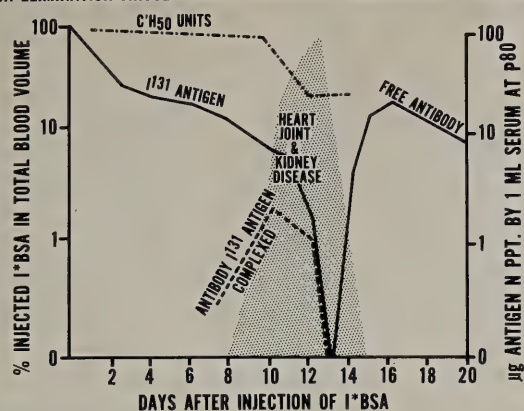


Chart 1.—The events after injection of 250 mg of I^{131} BSA per kilogram to produce acute (one shot), serum sickness in rabbits. The I^* BSA equilibrated over the first 48 hours and then disappeared at its catabolic rate. Antibody production, immune complex formation, depression of serum complement and immune elimination then occurred associated with the development of arteritis and glomerulonephritis.

Dixon^{7,8} established antibody production and immune complex formation leading to antigen elimination as the etiological events responsible for the vascular and glomerular lesions of acute serum sickness.

As in Chart 1, when 250 mg per kg of radio-labeled BSA was given intravenously to a rabbit, the circulating BSA declined rapidly over the first 48 hours as it equilibrated between the intra-vascular and extravascular fluid. The BSA then disappeared from the circulation governed by its non-immune catabolic rate. Anti-BSA antibody appeared on approximately the seventh day and combined with the BSA to form circulating complexes. The initial immune complexes were small because antigen was present in great excess and continued to circulate. As the amount of antibody increased, the immune complexes enlarged, fixed complement and were eliminated from the circulation, presumably by phagocytic cells. During this immune elimination, small amounts of antigen in immune complex form were filtered and accumulated in the GBM, apparently influenced by complex size, possibly antibody avidity, and the presence of vasoactive substances which increased vascular permeability. The amount of BSA antigen deposited was about 20 micrograms in the renal mass or approximately 4.4×10^8 molecules of BSA per glomerulus. The half disappearance time of the bound antigen from the glomerulus was about ten days, and the

sensitivity of the immunofluorescent technique in identifying the glomerular bound antigen was 0.25 micrograms of BSA per gram of rabbit kidney.⁹ The renal-bound BSA became undetectable by immunofluorescence in a few days and was apparently covered by anti-BSA antibody from the circulation which appeared after immune elimination. This may partly explain why glomerular-bound immune complex antigens are so difficult to identify by immunofluorescence.

When BSA was given to rabbits daily in amounts to balance antibody production, all rabbits which made immune responses (precipitating antibodies) developed overt glomerulonephritis after approximately two to six months of daily antigen injection. If the antigen dosage was not in balance with antibody production, injurious complexes did not form. Only minimal amounts of BSA representing .04 percent of the injected dose were deposited in the glomeruli daily before the onset of overt proteinuric glomerulonephritis. Somewhat before and coincident with the onset of proteinuria, the daily BSA immune complex deposition increased about 15-fold with values representing 0.5 percent of the injected dose. The half disappearance time of the BSA from the kidney (about five days) was similar before and after the onset of proteinuria.¹⁰

The striking quantitative increase in glomerular-immune complex material in proteinuric chronic serum sickness rabbits could be correlated with immunofluorescent findings. Typical light granular glomerular deposits of BSA tended to localize in the mesangium during the developmental phases of this lesion. The picture changed to one of heavy immune complex deposition predominantly along the GBM when the rabbit became proteinuric. This observation suggests that the phagocytic function of the mesangium may need to be altered before large amounts of immune complexes can accumulate in the GBM. It is of interest that these immune complex deposits can be dissolved out of the glomeruli by injecting huge excesses of antigen. Such a maneuver may have therapeutic implications in the future when specific antigens can be identified.

Multiple antigen-antibody systems may be involved in the formation of circulating immune complexes which can lead to the production of glomerulonephritis (Table 1); however, in human immune complex glomerulonephritis, the majority of the antigens remain unknown. For-

TABLE 1.—Antigen Antibody Systems in Immune Complex Glomerulonephritis

Exogenous (foreign) antigens
Foreign serum proteins, drugs
Infectious agents
<i>bacterial</i> —streptococcal, staphylococcal
<i>plasmodial</i> — <i>P. malariae</i>
<i>viral</i> —lymphocytic choriomeningitis, murine leukemia, Aleutian disease, lactic dehydrogenase, infectious equine anemia, Australian antigen.
?Majority as yet unidentified
Endogenous (autologous) antigens
<i>Nuclear proteins</i> —lupus erythematosus, New Zealand mice
<i>Thyroglobulin</i> —thyroiditis
<i>Renal tubular antigen</i> —Heymann's nephritis
?Majority as yet unidentified

eign or exogenous antigens and endogenous or autologous antigens are the two major categories. Foreign serum proteins and drugs are obvious examples of foreign antigens. The immune complex glomerulonephritis accompanying streptococcal infections, in which Treser and Lange¹¹ are now routinely demonstrating a glomerular-bound streptococcal membrane antigen, and the glomerulonephritis associated with infected atrio-ventricular shunts, in which glomerular-bound staphylococcal antigens have been identified, are good examples of foreign bacterial antigens involved in complex formation.¹² Plasmodial antigen has been identified in the immune complex glomerulonephritis that develops in children with quartan malaria.¹³

The frequency with which either spontaneous or induced persistent viral infections are associated with glomerulonephritis in animals deserves extra attention at this point. The best studied example is the lymphocytic choriomeningitis (LCM) infection of mice.¹⁴ The same general principles hold for the lactic dehydrogenase and leukemia viral infections of mice, Aleutian disease of mink and infectious equine anemia.¹⁵⁻¹⁸ When mice are infected neonatally with LCM virus, a persistent lifelong infection is established with a level of viral growth and viremia which varies with the mouse strain. Viral antibody complexes form and deposit along the GBM, producing a chronic, progressive glomerulonephritis. In intrauterine infections, the disease progresses more rapidly with glomerular-bound complexes and glomerulonephritis identifiable shortly after birth. The frequency of glomerulonephritis in

animals with persistent viral infections suggests that viral agents may play an important role in human immune complex nephritides of unknown cause; indeed, Australian antigen-antibody complex nephritis has been identified in man.

Endogenous or autologous antigens may also be involved in the production of either spontaneous or induced glomerulonephritis. The nuclear protein antinuclear protein immune complex nephritis of lupus erythematosus is the best example. Although lupus nephritis can be related to the presence of deoxyribonucleic acid (DNA) and anti-DNA antibodies, the possible contribution of cryoglobulins of the IgM rheumatoid factor type have also recently been implicated in renal immune complex deposits in the disease.¹⁹ A similar spontaneous disease in New Zealand mice has provided a useful experimental tool to study this type of immune complex nephritis.²⁰

Thyroglobulin anti-thyroglobulin immune complex nephritis has been produced experimentally, and at least two cases have occurred in humans. The possibility of precipitating nephritis in a thyroiditis patient who has circulating anti-thyroglobulin may help explain these observations.²⁴ This 5S pseudoglobulin of β mobility and 80,000 molecular weight possesses C3 convertase activity when activated by another, probably enzymatic, serum component and results in C3-9 consumption. Biologically active complement products, namely anaphylatoxins and chemotactic factors, may be generated by this mechanism without involving the classical C1,4,2 pathway.

Immunofluorescent identification of glomerular bound complement components suggest that some kidneys may contain only C3 and later acting components (C5,C6) without immunoglobulins, suggesting that the C3 proactivator system may be in action. IgG_{1,2,3}, IgG_{4b} and IgA can activate this system as well as naturally occurring bacterial lipopolysaccharides and yeast cell walls. Cobra venom factor, which is now widely used to deplete complement activity in experimental animals, also works through this alternate pathway by combining with the C3 proactivator protein. Work is now progressing to identify the C3 activating protein in the glomeruli in an attempt to correlate this with the observations of glomerular-bound properdin²⁵ and the presence of a C3 activator substance in the serum of these hypocomplementemic patients as described by Vallota and West.²⁶

Anti-GBM Antibody Glomerulonephritis

Glomerular injury produced by antibodies specific for the GBM, so-called anti-GBM antibody glomerulonephritis, is responsible for probably less than 5 percent of all immunologically induced glomerulonephritides. We have identified fewer than 60 cases in our own series of nearly 1400 patients. As early as the beginning of this century the nephrotoxicity of guinea pig anti-rabbit kidney sera was demonstrated in rabbits. In 1950 Krakower and Greenspan showed that the antigen necessary for the development of nephrotoxic sera resided in the GBM with cross-reactive antigens present in other vascular tissue. Current investigations in our laboratory have shown that the antigen is present in the non-collagenous portion of the GBM.

Glomerular injury produced by experimental heterologous anti-GBM antibodies can be divided into two phases.²⁷ The immediate or heterologous phase is produced by the direct toxic effect of sufficient quantities of antibodies fixed to the GBM. In the rat, 75 micrograms of antibody per gram of kidney or 1.2×10^{10} molecules of antibody per glomerulus are required for immediate proteinuria. Delayed or autologous phase glomerular damage may develop after even small doses of anti-GBM sera when host antibody to the foreign serum reacts with the glomerular bound heterologous anti-GBM antibody.

A second category of experimental anti-GBM antibody induced nephritis is that produced by the injection of GBM or basement membrane antigens in adjuvant. Sheep, for instance, develop a fatal anti-GBM nephritis following injections of human GBM in adjuvant. Circulating anti-GBM antibodies which accumulate in nephritic sheep following nephrectomy can be used to transfer this disease to normal sheep.²⁸

The causes of spontaneous anti-GBM antibody formation are unknown; however, several possibilities exist: (1) The presence of basement membrane antigens in both urine and serum²⁹ could serve as possible immunogens as suggested by the induction of anti-GBM nephritis by injection of the urinary GBM antigens in rabbits.³⁰ (2) Basement membrane antigens might also be altered or uncovered by toxins, infections or trauma. The recent description of anti-GBM nephritis following an influenza A2 infection³¹ supports this concept. (3) Exogenous antigens which cross-react with the GBM may also be im-

portant. Once anti-GBM antibody is formed, it can react with the GBM. Heterologous anti-GBM antibodies which were only of experimental interest until recently have now been found in certain anti-lymphocyte globulin (ALG) preparations, probably induced by the inclusion of vascular fragments in the lymphocyte inoculum.³² These GBM-reactive antibodies in ALG are capable of producing acute nephritis in primates and are potentially hazardous to transplant patients. When anti-GBM antibodies (heterologous or autologous) fix to the GBM, glomerular injury ensues either through the complement-PMN pathway or by some as yet undefined mechanism.

In 1967, Lerner, Glasscock and Dixon³³ reported a series of patients with nephritis and linear deposits of immunoglobulin and complement along the GBM. Substantiation of the etiological role of this anti-GBM antibody came when glomerulonephritis was transferred to a renal homograft placed in one of these patients who had circulating anti-GBM antibodies detectable following nephrectomy.

Anti-GBM antibodies may produce a variety of clinical lesions and courses in humans. The most common course is that of rapidly progressive glomerulonephritis; and when the nephritis is accompanied by pulmonary hemorrhage, the condition has been termed "Goodpasture's syndrome."^{34,35} Since hemoptysis can be a feature of other systemic illnesses with renal involvement and may occur as a complication of uremia, the term "Goodpasture's syndrome" should be used only for those patients who have evidence of anti-GBM antibodies. The pulmonary involvement seen in patients with anti-GBM nephritis suggests a common immunological mediator. Indeed, anti-lung antibodies are capable of producing glomerulonephritis. Immunoglobulin has been identified by immunofluorescence along the alveolar septum in patients with Goodpasture's syndrome,³⁶ and antibodies cross-reactive with the GBM can be eluted from the lung tissue of such patients.³⁷

Anti-GBM antibody mediated nephritis may be diagnosed tentatively by detecting immunoglobulin bound to the GBM in a smooth, continuous linear pattern by direct immunofluorescence. The specificity of the linear immunoglobulin deposits can be confirmed by eluting the antibody from washed renal cortical homogenates with acid pH and demonstrating its fixation to normal human

kidney *in vitro* or to animal kidney *in vivo*. This specific proof is becoming necessary because linear deposits of immunoglobulin have been found rarely in non-nephritic autopsy kidneys and some kidneys from patients with lupus erythematosus and diabetes. Elution studies have not confirmed the presence of anti-GBM antibodies in this latter group of kidneys.

Circulating anti-GBM antibodies³⁸ may also be detected in some patients with anti-GBM nephritis, and testing is useful to confirm the diagnosis and also to follow the patient before renal transplantation.

In summary, glomerulonephritis may be caused by antibodies capable of reacting directly with antigens in or on the GBM, so-called anti-GBM antibodies, or may be produced by the glomerular deposition of circulating nonglomerular antigen-antibody complexes. Once the immunoreactants lodge in the glomeruli, mediation pathways of immunological injury common to both mechanisms can result in glomerular damage. The histological damage and clinical picture of the patient are not determined so much by the immunological mechanism but rather by its kinetics and the host response to it.

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Important Advances in Clinical Medicine

Epitomes of Progress -- Plastic Surgery

The Scientific Board of the California Medical Association presents the following inventory of items of progress in Plastic Surgery. Each item, in the judgment of a panel of knowledgeable physicians, has recently become reasonably firmly established, both as to scientific fact and important clinical significance. The items are presented in simple epitome and an authoritative reference, both to the item itself and to the subject as a whole, is generally given for those who may be unfamiliar with a particular item. The purpose is to assist the busy practitioner, student, research worker or scholar to stay abreast of these items of progress in Plastic Surgery which have recently achieved a substantial degree of authoritative acceptance, whether in his own field of special interest or another.

The items of progress listed below were selected by the Advisory Panel to the Section on Plastic Surgery of the California Medical Association and the summaries were prepared under its direction.

Reprint requests to: Division of Scientific and Educational Activities, 693 Sutter Street, San Francisco, Ca. 94102

Craniofacial Osteotomy

DEFORMITIES OF THE CRANIOFACIAL skeleton, previously considered untreatable, are now partially amenable to surgical reconstruction. Techniques have been developed for correcting hypertelorism and maxillary malposition frequently associated with many congenital anomalies or traumatic injuries. These complex problems require a multidisciplinary team approach. Considerable preoperative planning by the plastic surgeon, neurosurgeon, ophthalmologist, and orthodontist

is essential. In the most severe cases the treatment of ocular hypertelorism requires a combined cranial and facial approach.

The cranial facial operation may involve resection of the cribriform plate or ethmoid sinus as well as osteotomy through the orbits, anterior cranial fossa, zygoma and maxilla. For example, patients with Crouzon's disease often have a severe degree of maxillary hypoplasia. The underdevelopment of the orbital floor and rim may lead to severe degrees of proptosis that produce a grotesque appearance and leave the cornea extremely vulnerable. They are treated by a combination of midfacial osteotomy, bone grafts, silastic implants and soft tissue plastic surgery.

Mandibular osteotomy, as routinely used in

the treatment of prognathism or retrognathism, may be combined with craniofacial osteotomy in order to obtain more desirable occlusion and facial proportion. The osteotomy and dental occlusion are based on accurate preoperative dental models and facial cephalometrics. There are many alternative osteotomies, vertical, horizontal and sagittal, the type being dependent upon the specific clinical situation and the preference of the surgeon.

ERNEST N. KAPLAN, M.D.

DOUGLAS K. OUSTERHOUT, M.D.

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Subcutaneous Mastectomy

THE INDICATIONS for subcutaneous mastectomy are: severe cystic disease, with or without frequent biopsy; unremitting mastodynia; fibrous diseases of the breast; positive family history of breast cancer with progressive nodularities; and histological examination revealing intraductal disease or sclerosing adenosis.

Subcutaneous mastectomy entails extirpation of the mammary gland with its tail, while preserving the skin and nipple. The breast is then reconstructed by suitable prosthesis. The operation can be precarious. If the circulation of the skin brassiere and nipple are compromised, necrosis can occur, precluding esthetic reconstruction of the breast.

VINCENT R. PENNISI, D.D.S., M.D.

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Important Advances in Microsurgery

EXPERIMENTAL AND CLINICAL microsurgery has progressed on several fronts in the past year. Furnas was able to achieve a 90 percent immediate success rate with the replanting of legs in puppies. He used these animals to study bone growth, which was found to be almost normal. Information of this type is of basic importance, in the light of proven feasibility of extremity replantation in man. Seven of the patients in 60 documented cases to date were under seventeen years of age. O'Brien, Lendvay, and Owen of Australia reported remarkable success replanting traumatically amputated digits. Their results parallel those of the mainland Chinese, who claim to have successfully replanted 40 digits in 43 attempts. McKee has transplanted a segment of rib by microvascular anastomosis to reconstruct defects in the mandible in both dogs and humans. Kaplan and others are developing techniques for outlining flaps in humans for immediate transplantation for reconstructive purposes. Buncke and McLean have explanted a segment of the omentum from the abdomen to the scalp for total ear reconstruction in the dog, and to fill a 9- by 10-inch soft tissue defect of the scalp in one human case. The omental vessels were anastomosed to the superficial temporal vessels. A free skin graft was placed over the transplanted omentum and took without problem, creating in effect a prefabricated laminated flap.

Several companies are now marketing inexpensive, light and mobile binocular operating microscopes that provide seven to ten diameters magnification. With these simplifications in technique and added interest in the field, immediate tissue transplantation by microvascular anastomosis will undoubtedly continue to expand.

HARRY J. BUNCKE, JR. M.D.

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Facial Reanimation

THE ARMAMENTARIUM FOR SURGICAL treatment of permanent facial paralysis is rapidly growing with many recent new developments. Individual variations of skin tone, age, completeness of paralysis and associated other sensory and motor nerve involvement require tailoring of the variously available surgical procedures to the individual patient's needs. Time tested techniques such as temporalis muscle transfer to reanimate the eyelids, lateral tarsorraphy, supra-brow and nasolabial skin excisions and XII nerve transplant are all extremely useful in selected patients.

Newly developed techniques, such as gold weights to help close the upper eyelid and silicone rubber slings surrounding the palpebral fissure, all hold considerable promise. The most recently introduced procedures include VII nerve crossover grafts, using a sural nerve graft to bridge from the normal side to the paralyzed side. Also newly reported are free muscle grafts, using the short toe extensors onlaid onto functional muscle with the tendons aligned to reanimate the paralyzed side. These newer procedures are extremely promising but will require the test of time to prove their efficacy.

GARRY S. BRODY, M.D.

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Undesirable Side Effects Following Intralesional Corticosteroid Therapy

INTRALESIONAL INJECTION of keloids with corticosteroid preparations was first advocated in 1951 but it was not until after the introduction of triamcinolone acetonide (Kenalog®) in 1961 that the use of this type of therapy became popular. Triamcinolone diacetate (Aristocort®) and

betamethasone (Celestone®, Soluspan®) are also reported as effective agents but they are employed less commonly than Kenalog.

Unfortunately, the widespread use of these agents has led to indiscriminant use leading to an increasing incidence of side effects.

Systemic reactions such as syncope, anxiety, profuse sweating, chest and back pain and collapse have been described.

Plastic surgeons are seeing the undesirable local side effects more frequently each year. The most common of these are excessive atrophy of the surrounding subcutaneous tissues along with changes in pigmentation. Both hypo-pigmentation and erythema may occur with hypo-pigmentation being more common.

In addition, dermatologists are employing intralesional corticosteroid therapy in a multitude of skin disorders, including granuloma annulare, alopecia areata, lichen simplex chronicus, psoriasis, chronic eczema, discoid lupus erythematosus, herpes simplex, and acne "nodules."

Although it is not always true, local adverse reactions generally follow the use of excessive dosages of triamcinolone. Definite standards of treatment and dosage schedules should be followed to minimize these adverse reactions. First of all, strict sterile technique must be adhered to. Second, care must be taken so the agent is injected only intralesionally with no injection into the surrounding or deep subcutaneous tissues. Thirdly, dosage schedules should be followed. The following schedule, which was evolved at the University of Kansas during the treatment of over 500 keloids can be recommended.

Adults: Maximum dose, 120 mg—may be repeated once a month for six months.

Lesion—1 to 2 square cm—20-40 mg; 2 to 6 square cm—40-80 mg; 6 to 10 square cm—80-100 mg

Children: Maximum dose, each treatment:

1 to 2 years of age—20 mg; 3 to 5 years of age—40 mg; 6 to 10 years of age—80 mg

WILLIAM J. MORRIS, M.D.

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Porcine Skin Grafts

THE BENEFITS OF HOMOGRAFT skin on burn wounds in restoring the water vapor barrier, decreasing protein losses in wound exudate, decreasing wound sepsis, relieving wound pain, increasing epithelialization in second degree burns, and for use after eschar separation to produce healthy, clean granulations for autografting have been known for many years.

Because of its limited availability, the initial users left the homograft skin in place until it was rejected. The rejection mechanism negated the initial beneficial results. The rejection process was eventually avoided by the use of homograft skin as a temporary biological dressing which was replaced at intervals of one to five days.

Whenever the demand for a temporary biological dressing arises, despite the urgency, it is often difficult to obtain an adequate supply of suitable tissues whether from living donors, cadavers or tissue banks.

This need for human skin substitutes for burn victims prompted many investigators to search for materials from animal sources. Porcine skin heterograft was found to be an excellent substitute for homograft skin. Since the early 1960's, porcine skin has been used only to a limited degree in the care of burn patients because of the cost and the many problems encountered in harvesting skin from live pigs or from hides obtained from local slaughtering houses.

In 1969, the Burn Treatment Skin Bank, Inc., in Phoenix, Arizona, was organized to supply fresh porcine dressings. With the normal 24-hour air express delivery time, the Burn Treatment Skin Bank has become a heterograft skin bank for the entire United States medical community.

Porcine skin is cut with a pneumatic dermatome in strips 3 inches wide by 4 feet long by .015 inches thick. The strips are treated with Betadine® (povidone-iodine) and neomycin solutions, rolled on sterile gauze backing, and sealed in double plastic bags. It is then stripped on ice in insulated containers and should be

stored at 4° C. It is recommended that the skin be used within ten days after processing.

The use of porcine skin as a temporary biologic dressing for burns has become a widely accepted practice. It is applied as one would apply homograft skin. However, because it is readily available, surgeons have been able to extend its uses—for example, over donor sites, on second degree burns and over mesh grafts. It has also been used effectively in treating open soft-tissue wounds, surgical infections and wounds where primary closure is delayed.

In contrast to homograft skin it may be left in place for extended periods of time because it does not become vascularized and does not elicit a significant inflammatory response.

There is no doubt that the commercial availability of porcine skin for the treatment of large skin wounds will aid in the saving of many lives.

ANGELO CAPOZZI, M.D.

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Hypospadias

LONG-RANGE STUDIES evaluating various techniques of hypospadias repair and management have pointed out certain important conclusions. The objective is to produce a full length penile urethra, expansile and extensible, without chordee, providing a urethral channel of adequate bore. There should be no pockets or adnexal components in the newly formed urethra.

The most common type, distal or frenular hypospadias is repaired as a single stage procedure done at age four and a half to six years. This is a modified circumcision, utilizing a portion of the prepuce to elongate the foreshortened urethra out to the distal glans. In the penile, peno-scrotal and perineal types, when the chordee is severe and the genitalia hypoplastic, a two-stage operative plan is indicated. The first operation is done at age one to three

years. This consists of chordee release and transposition of the prepuce flaps to the penile ventrum. This allows the penis to develop properly before urethroplasty at age four and a half to six.

In every instance the complete repair can be accomplished using only local tissues. The use of skin flaps, scrotal flaps, free skin grafts from extragenital areas is unnecessary. When skin has been lost following previous operation, there may be a need to bring the skin from other areas. Only the penile skin, transposed from the prepuce, will provide fully expansile, smooth and adnexal free lining for urethroplasty.

It is mandatory that this be utilized efficiently and carefully to replace the absent urethra. Stenotic or patulous urethra, urethral hairs and pockets will result from improperly selected type and technique of repair.

ROBERT E. BERNER, M.D.

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Use of the Water Bed

IN SPITE OF WIDESPREAD attention to proper nursing and local wound care, pressure sores continue to present a problem to many physicians in diverse fields. Once a pressure sore is established, its cure will often require many months in hospital at great monetary and psychological expense.

Clinical data is accumulating that the use of the "water bed" can prevent the formation of pressure sores and hasten the healing of established ulcers. Pressure sores result from tissue ischemia, usually the result of prolonged pressure on tissues overlying bony prominences or lateral shearing and stretching of blood vessels to the tissue.

The water bed solves the problem by equal distribution of the patient's weight over the greatest possible surface. The patient floats in a controlled volume of water, and all body

points contact the water at less than capillary pressure. Thus, capillary circulation continues unabated, nourishing even tissue that overlies bony prominences.

The water bed represents an important advance in the care of patients with paraplegia, stroke, spinal cord injury and geriatric problems. In addition, it can be utilized to simplify nursing care and minimize patient discomfort, as patients can be placed directly on their pedicle flaps or skin grafts without damage of slough from excessive pressure.

DONALD R. LAUB, M.D.

RICHARD J. SIEGEL, M.D.

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The Doppler Flow Meter

THE DOPPLER FLOW METER IS A relatively new and simple instrument that has found many applications both in clinical medicine and in research. The basic function of the instrument is to emit ultrasound and to detect reflected ultrasound. Reflected sound from stationary objects (for example, bone) is unchanged in frequency, whereas sound reflected from a moving object (such as blood cells) will change in frequency by an amount related to the velocity of the particles (the Doppler effect).

The flow meter has a "probe" consisting of a piezoelectric crystal which generates the ultrasound beam. A second crystal, slightly separated from the first one, detects the reflected ultrasound. The probe is applied to the skin in close contact using "electrode" jelly. The ultrasound is translated into audible sound, and the pulsations in the vessel are heard. Since the change in frequency is related to velocity, this can also be translated into vessel caliber.

Clinical uses for the Doppler Flow Meter include:

- Pulse monitoring during surgery;
- Evaluation of arterial obstruction secondary to atherosclerosis, spasm or injury;

● Identification of perforating vessels in vari-
cosities;

● Assessment of blood flow in tissue damage
—for example, frost bite;

● Assessment of blood flow to pedicle flaps as
an indicator of viability and as an aid to timing
of delay and separations.

The use of this simple device obviates the
need for injection of dye indicators, isotopes and
other relatively complicated or potentially harm-

ful materials that have been described for the
same purposes.

ERNEST N. KAPLAN, M.D.

LARS M. VISTNES, M.D.

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Loma Linda University

School of Medicine

Disorders of Platelet Function

PROGRESS IN OUR UNDERSTANDING of platelet physiology has led to the recognition of clinical conditions in which one or more disturbances of platelet function result in a hemorrhagic disorder. Among the important advances are: *in vitro* techniques for studying platelet aggregation produced by various pharmacologic stimuli, biochemical evaluation of nucleotide metabolism, and measurement of the clot-promoting potential of aggregated or reagent-damaged platelets (also called platelet factor 3 (PF-3)). Abnormalities in these *in vitro* test systems are frequently but not consistently correlated with a disturbance in hemostasis in the patient.

In general the bleeding observed in platelet disorders is rarely of a life-threatening nature or spontaneous. It is usually related to trauma and episodic. Hemorrhage into the skin of varying severity is the most common problem, and this is followed in frequency by epistaxis, menorrhagia, hematuria, and rectal bleeding. It should be stressed, however, that platelet disorders are not common, and when a patient presents with these signs and symptoms a "platelet disease" should not be among the first considerations in the differential diagnosis. This is especially true in children and adolescents, where the neoplastic hematologic diseases, idiopathic thrombocytopenic purpura (ITP), and hereditary disorders of coagulation should be ruled out first. As always, a methodical history from the patient or the family is of prime importance. The type of bleeding experienced (spontaneous or traumatic), the age of onset, the occurrence of hemarthrosis, a history of postoperative hemorrhage, should all be initially discerned by the physician. The patient must be questioned closely with regard to drug ingestion—with particular reference to aspirin. In our experience many persons do not

regard aspirin as a drug or medication, but rather as something as commonly ingested as food.

The early response of platelets to vascular damage or injury is one of adhesion, rapidly followed by aggregation and concomitant release of nucleotides such as adenosine diphosphate (ADP). Other substances, such as serotonin, can also be found in the plasma environment. Platelet membrane lipoprotein is then capable of catalyzing reactions of the coagulation sequence, which is also activated by contact with the vascular subendothelium exposed to plasma during the vascular insult. Thrombin formation results in "consolidation" of the hemostatic platelet plug, as manifested by its contraction into a firm mass, and in reinforcement with fibrin. Platelet disorders may be a manifestation of a defect in or absence of any one of these steps. For example, in thrombasthenia platelets do not respond to exogenous ADP. Yet if collagen or thrombin is added to the platelets of these patients, normal amounts of ADP are released. Thus, it is possible to speculate that the thrombasthenic state is one in which the platelet membrane is unresponsive to ADP although it allows its passage to the exterior. In addition, clot retraction is poor to absent, and platelet fibrinogen is low. The prolonged bleeding time seen clinically may very well be a direct consequence of the inability of the patient's platelets to respond to ADP.

Recent concepts relating platelet size and function to platelet age have been utilized by Dr. Sahud, whose review appears elsewhere in these pages, as the basis for a new classification of platelet disorders. It has been suggested that young platelets are larger in size and metabolically more active than older platelets. Dr. Sahud reports that in normal subjects 8 to 14 percent of the platelets are larger than 2.5μ in diameter (large forms). Thus, platelet disorders in which large forms fall within this range are said to be associated with euthrombocytes; disorders in which the percentage of large forms is less than

8 are classified as being associated with microthrombocytes; and if more than 14 percent of the total number of platelets are large forms, the disorder is classified as associated with macrothrombocytes. Although this novel approach is of great interest, its quantitative aspects will need further clarification and more precise definition. More consideration and emphasis might be given to the number of *normal* platelets in the samples under study. There are many clinical conditions not associated with abnormalities in platelet function in which the percentage of large forms far exceeds 14.

The problem of hemorrhage in uremia has been considered in some detail. This discussion is both timely and time-worn. We would suggest that chronic renal disease is representative of several situations in which the correlation between abnormal *in vitro* laboratory tests and clinically significant bleeding leaves something to be desired. Uremic patients who show such defects as poor platelet aggregation or abnormal prothrombin consumption may never develop a bleeding tendency in the course of their disease. Furthermore, the majority of patients studied thus far were not actively bleeding at the time of evaluation. Since dialysis has been shown to correct the abnormal laboratory findings, it now seems clear that the various toxic-metabolic products which accumulate in uremic plasma can interfere with *in vitro* and possibly *in vivo* platelet function. We find it difficult to incriminate only one of the many toxic agents in uremia as being responsible for the hemostatic defect. Finally, it should be mentioned that thrombocytopenia should not be overlooked as a factor contributory to the impaired hemostasis in uremia.

The newly characterized platelet disorder known as "storage pool disease" (also called "familial ADP release dysfunction") is discussed. The non-metabolic adenine nucleotide storage pool is diminished in the platelets of these patients, and thus aggregation in response to agents like ADP, collagen and epinephrine is defective, particularly with regard to the "second wave" which is dependent upon release of intrinsic ADP from the platelets. In Dr. Sahud's scheme of classification, the disorder appears to be characterized by the presence of small platelets in addition to the aforementioned defects. Although there is some superficial clinical resemblance to

the defect produced by aspirin, there is a difference in the mechanism involved. Following aspirin ingestion there appears to be a "block" in the release of ADP from the storage pool. These patients actually show a quantitative decrease in this storage pool; and thus if they ingest aspirin they would theoretically superimpose another defect upon the preexisting one.

It is worth while to emphasize the closing remarks of Dr. Sahud's review. Before a diagnosis of a platelet disorder is definitively made, all other more common causes of a hemorrhagic disorder should be ruled out, and the *in vitro* tests should be repeated at least once under conditions of drug abstinence.

AARON J. MARCUS, M.D.
Chief, Hematology Section
New York VA Hospital
Associate Professor of Medicine
Cornell University Medical College
New York City

Health Care in the Decisive 1970's

Where We Stand and Some Lessons

ONE-FIFTH OF THIS IMPORTANT and decisive decade for health care has now passed. An assessment of where we stand seems in order and there may be some lessons to be learned. At first glance at least, the problems seem still to be major and the progress toward their solution so far relatively minor. There seems to be a growing awareness of the enormity of the task this nation has set for itself in health care, and the overall approach seems to be a little more cautious and conciliatory than sometimes was the case in the past. There seems to be a trend away from actions which seek to impose the will of one group upon others, and toward collaborating to find solutions which will be workable and reasonably satisfactory to all concerned. But so far this is only a tendency. The need for real collaboration has yet to be fully perceived in many quarters, and the mechanisms which will be necessary to accomplish it have yet to be devised.

For example, the philosophical approaches of conservatives, liberals, and radicals alike to the problems of health care delivery seem to be

softer. No longer does it mean much to say that health care is available and that anyone who needs it can get it, or that health care should be provided for the less fortunate segments of our society in the form that someone else thinks is good for them, or to say that the whole system is so rotten and inefficient that it should be completely destroyed and a new start made. Nor can those who hold any of these views any longer afford to maintain that they and only they are right and everyone else is wrong. These realities are now only just beginning to be perceived and their implications for a new collaboration among all those properly concerned in health care, including government, have yet to be widely recognized.

The records of those who have tried to solve the problems of health care delivery have so far not been very good. Some would have us copy one or another of the systems used in foreign countries but this has not attracted much support. The efforts in public health circles to subsume health care delivery into public health have not succeeded. The prepaid closed panel group practice advocates have earned a degree of acceptance but their plans have not swept the country. Hospital-based prepaid plans do not seem to have caught on to any extent. Medical Society sponsored foundations for health care seem to be gaining ground but these too have not yet found themselves on the crest of a wave. Perhaps this is because physicians, whose active participation is essential to these programs, are always reluctant to surrender any of their independence or freedom of action to anyone. Government programs to date have seldom been as effective as their sponsors had hoped, with the possible exception of Medicare (Title XVIII of the Social Security Act) which has actually worked out somewhat better than many expected it would. Some kind of national health insurance now seems likely to be enacted, and what this will be like and whether it will be workable and satisfactory to consumers, providers, payors and government, and whether it will actually make more or less health care services available to the people of this nation remains to be seen. The chances of success would seem greater, however, if those who must carry out the plan and render and receive its benefits, were more in evidence in the developmental processes which must now be taking place.

The emphasis of government so far in the 1970's seems to be more upon the quantity and less upon the quality of health care services. In fact the California State Plan for Health actually redefines quality more or less in terms of quantity and distribution of services. This emphasis is also to be seen in the extent to which governmental support of medical schools has become more and more conditional upon increasing the quantity even at the expense of the quality of the product, as when premiums are offered to medical schools for graduating more students and for doing this more quickly with a shorter curriculum. One may suspect that here again a single segment of society—this time the federal bureaucracy—is deciding what it thinks is best for the rest of society and trying to impose its will with little or no collaboration with those segments which will be affected both in the short and long term by the actions taken.

The 1970's so far have found no real solution to the problems of rising costs of health care services. It has become all too evident that rising costs have been an inevitable result of success in rendering more services of higher quality to more people, of success in eliminating debasing charity for patients, and of success in raising the wage scales and working conditions of those in health care so as to achieve parity with workers in other fields. Obviously, neither the degree of success nor the amount of the cost was anticipated. So far, approaches to reducing costs have been both crude and paradoxical. For example, at the national level funds for research have been diverted in order to provide more services. The effect of this is to reduce research into the cause, nature and eradication of illness and injury, and into the cost benefit and cost effectiveness of various health care services, both of which might in time reduce costs significantly, while at the same time increasing costs by providing more services for more people which more research might indicate they may or may not need. And at the state level both the number and type of services for the needy were arbitrarily curtailed by fiat. This quite ruthless approach was subsequently struck down by the court. More rational, realistic and sophisticated approaches to the problems of costs are clearly needed.

It is suggested that among the lessons to be learned from the experience so far is that no

single philosophical approach and no single segment of health care, including government, can alone develop approaches or solutions to health problems and then impose them on the rest without the risk of costly disruption and general dissatisfaction. Just as consumers have clearly indicated they must be part of the planning, operation and evaluation of services if they are to accept them and be satisfied, it will surely be found that physicians, other providers, payors and many other elements of the health care industry will also have to be involved if they too are to accept the services and be satisfied. Dissatisfaction and nonacceptance, whether of providers or consumers, can be disruptive, costly and counter-productive of the goals everyone seeks to achieve. If all this is true, as seems likely, and if it is not generally perceived for some time, which also seems likely, then there will be a further period of blundering, bludgeoning, dissatisfaction and waste until the necessity is recognized for new and much more collaborative approaches to planning, operations and evaluation for health care delivery programs and systems which will enable not only consumers, but physicians, other providers, payors and all who are properly concerned to be properly involved. It is suggested that recognizing this, which must be done, and developing the means to do it are now most pressing problems which should be highest on the health care agenda for the next year or two of this decisive decade.

—MSMW

Gastroduodenal Stress Ulcers

THE SPECIALTY CONFERENCE from UCLA on gastroduodenal "stress" ulcers [page 32] serves to emphasize the obscure and diverse etiology of these lesions as well as the difficulties encountered in treating them. Stress ulcers are a form of peptic ulceration and occur in patients already desperately ill as a result of injuries, operations or trauma to the brain; thermal burns; or acute, severe illnesses. Perhaps it is more precise to refer to these lesions as acute peptic ulcers associated with stress or as Doctor Schwabe stated, "the stress ulcer syndrome." Peptic ulcers oc-

curing with stress more often are located in the stomach than the duodenum, are frequently multiple, and are most likely to bleed or perforate. Furthermore, except when the ulcers occur with central nervous system lesions, most of the patients do not have gastric hypersecretion.

It is likely that a variety of causes or combinations of circumstances are involved in the acid-peptic digestion occurring in stress ulceration and that these operative factors vary from one patient to another. Although the precise cause of the peptic ulceration or erosion is not known, the results of these lesions are well enough understood to allow a rational approach to diagnosis and treatment.

Theoretically, stress ulcers may be prevented in some instances by the recognition and treatment of predisposing causes. In the clinical setting of a poor risk patient severely traumatized or chronically stressed, a prophylactic ulcer regimen, without the administration of anticholinergic drugs, may be helpful. Once bleeding becomes manifest and the nature of the lesion is established, both the surgeon and the gastroenterologist should collaborate to determine the best mode of management in each case. Although many of the patients are exceedingly poor operative risks, it should be remembered that they likewise sustain hypovolemia and continued bleeding equally poorly. Lucas et al¹ found that of more than 300 patients who had significant bleeding, over 80 percent responded to ice-saline lavage of the stomach and only 38 required operative intervention. I believe that the indications for operative treatment when bleeding continues are similar to those when gastrointestinal hemorrhage is due to other causes. Dunphy and Hoerr² in 1948 emphasized that the timing of operation in patients with acute gastrointestinal hemorrhage is related to the rate of bleeding as manifested by the response to transfusion. They found that if the blood pressure could not be stabilized initially by the administration of 2000 ml of blood or if after stabilization it was necessary to transfuse more than 1000 to 1500 ml daily, the patient was unlikely to respond and prompt operation was indicated. These same criteria seem as important now as they were then.

In the Specialty Conference, Doctor Clarke clearly outlined the variety of operative procedures employed to treat patients with massively

bleeding acute gastroduodenal mucosal ulcerations. No one operation will suffice for all circumstances and the proper selection will depend primarily upon the patient in relation to his general condition, predisposing causes, and the operative findings. There is less uncertainty with regard to management when stress ulceration is complicated by perforation. Prompt operation with simple closure and omental reinforcement with or without vagotomy and pyloroplasty are indicated. When huge perforations are present, gastric resection becomes necessary.

At present, "stress-ulceration" is a nondescript term referring to acute gastroduodenal mucosal ulceration in a heterogeneous group of patients. For this reason treatment, too, must be highly individualized.

EARL F. WOLFMAN, JR., M.D.

*Professor and Chairman
Department of Surgery
School of Medicine
University of California, Davis*

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National Education Week on Smoking

THE NATIONAL and California Interagency Councils on Smoking and Health have designated January 9 through 15, 1972 as National Education Week on Smoking. As a component member of The Interagency Council, the CMA has a special responsibility to participate in this week-long effort to further publicize and emphasize the health hazards of smoking.

There should be no further need to detail for physicians the latest findings linking smoking and disease. Since the historic first report in 1964, the Surgeon General has issued four supplemental reports further corroborating and extending the original conclusions. Encouraging statements of commitment and exhortation have issued from the World Health Organization and the AMA; our own CMA at its 1971 meeting passed resolutions declaring opposition to smoking in all public places and in CMA sessions, and urging the elimination of cigarette advertising from all

media. Meanwhile the ban on tv and radio cigarette advertising took effect on January 2, 1971, presumably heralding a new era of public and governmental activism in the campaign to educate and thereby protect the citizenry against what many authorities consider our worst public health hazard.

Despite these encouraging portents, accompanied by indications that many millions have indeed given up smoking, we must acknowledge that many other millions have meantime become newly addicted and re-addicted to smoking. Smoking incidence remains disturbingly high among the poor and uneducated, has fallen off relatively little in women, and is actually rising among teen-agers. Concurrently the indomitable cigarette industry inexorably grinds out new and ingenious advertising approaches which effectively vitiate the fading impact of the tv and radio ban and the Surgeon General's reports.

In this context, what is the physician's responsibility? Beyond repeatedly urging our patients to cease smoking (advice which is still unfortunately neither given nor much less heeded consistently) surely there are other avenues to be taken, some quite close to home, and other more adventurous routes to physician involvement in community and political activity. Certainly at the local level, the surface has barely been scratched. How many County Medical Societies have seriously tried to influence the public smoking activities of their members? Is it surprising if many smokers (and especially children and teen-agers) are cynical and skeptical about our warnings, when physicians puff in public, when profitable cigarette machines remain virtually unassailable in hospitals and other health facilities? These are obvious areas for physician leadership. There are some other directions: physicians might more actively petition and pressure their legislative representatives at local, state and national levels for more effective curbs on advertising, more protection for the rights of non-smokers, and elimination of subsidies for tobacco growers. Many physicians are conscientiously engaged in such activities; many more are needed in order to demonstrate, convincingly, our professional commitment and implement our knowledge and convictions about the unconscionable damage to the public health from smoking.

JACK LEIBMAN, M.D.

*Chairman, San Francisco
Interagency Council on
Smoking and Health*

CASE REPORTS

Refer to: Saenz L, Mottram M: Avulsion of ischial apophysis. *Calif Med* 116:64-68, Jan 1972

Avulsion of Ischial Apophysis

LEONEL SAENZ, M.D. AND

MARTHA MOTTRAM, M.D. *San Francisco*

INJURIES TO THE ISCHIAL apophysis are uncommon but are associated with recognized clinical and x-ray features. The present report is prompted by referral to our x-ray department of three patients, two of whom had a provisional diagnosis of "bone tumor" made elsewhere.

Apophyseal injuries are also identified by numerous terms such as avulsion of the apophysis, epiphyseolysis, avulsion fractures, epiphysitis secondary to trauma or osteochondritis. Apophyseal avulsion is descriptive and we consider it the proper term. A fragment of ischium may be avulsed along with the secondary center, but the diagnosis and treatment are identical in both instances.

The secondary center for the ischium ossifies in the mid-teens and unites at 19 to 21 years of age. When the center is first ossified and visible on the films it is either a thin linear crescentic shadow or consists of several separate calcified centers which later coalesce. The apophyses on the two sides may be asymmetrical in appearance and date of ossification. In the seven-year interval between 14 and 21 the center is vulnerable to avulsion. The adductor magnus, the long head of the biceps femoris, the semimembranosus and the semitendinosus attach to the tuber-

osity. The injury responsible for the avulsion is one that causes a sudden tension or pull on the hamstring muscle or adductor magnus. This occurs when the leg is forcibly abducted and the thigh flexed. In teenagers this injury frequently occurs during strenuous sports such as basketball, highjumping, running or hurdling. At the time of injury there is usually sharp, severe pain aggravated by stretching the thigh, with muscle spasm and weakness. Limping is commonly present. The ischial area may be swollen and tender. In most reported cases there is immediate disability and limitation of activity, but an occasional patient will not recall a specific disabling injury or will have only slight discomfort. All pain and tenderness may clear completely, but often there are chronic or intermittent symptoms. One of our patients with an old injury had pain only on sitting, a feature that has been noted in other cases.¹ Weight-bearing or stooping may aggravate the pain. The sciatic nerve may be irritated, especially when there is non-union and bony overgrowth.²

Films immediately following injury may show partial or complete apophyseal avulsion, or avulsion of this center plus a fragment of ischium. When there has been an old injury with an ununited fragment, x-ray films show bony overgrowth not only on the ischium but also on the margins of the avulsed fragment, resulting in a large, irregular, bony mass which may be fused to the ischium or remain as a separate bony mass or have fibrous union. Soft tissue calcification often occurs in the adjacent tissues. We have seen three additional patients with asymptomatic overgrowth of the ischium noted as an incidental finding. After an injury when the secondary center has not yet ossified, there may only be a little irregularity of the inferior margin of the ischial tuberosity, mottling and loss of sharp definition of the cortex.

Treatment in acute cases is symptomatic, with bed rest advised for about two weeks and then

From the Orthopedic Department, St. Joseph's Hospital, San Francisco.

Submitted December 18, 1970.

Reprint requests to: M. E. Mottram, M.D., 450 Sutter Street, San Francisco, Ca. 94108.



Figure 1 (Case 1).—A—Bony proliferation on the lateral inferior aspect of the right ischium, measuring 1.5 and 5.5 cm. B—Nineteen years after surgical removal of an avulsed ischial apophysis.

ambulation with crutches and limited activity for about six weeks; strenuous activity should follow bony union. Heat often relieves the discomfort. In late cases, treatment depends on the extent of clinical symptoms and disability. Some patients have few complaints, even with a large mass of bone, and need only occasional rest periods and heat for prolonged relief. Others may have sufficient disability, with pain and pressure symptoms, to warrant removal of the bony mass and re-attachment of the tendons. It may prove difficult to remove the mass without recurrence and reossification in the adjacent soft tissues (Case 2).

The following three cases are included to demonstrate the roentgen changes and problems in management.

Reports of Cases

Case 1. The patient was a 16-year-old boy when admitted to hospital in June 1949 because his family physician had diagnosed a bone tumor on physical examination when a large bony mass was palpable in the buttock. Six months earlier, he had fallen in a sitting position. After initial slight pain there was no further discomfort. Films show (Figure 1A) bony proliferation on the lateral inferior aspect of the right ischium measuring 1.5 cm by 5.5 cm. There is a mottled pattern and a moderate degree of irregularity of outline, part of which may be a result of calcification of the adjacent epiphyseal plate. The large bony mass was resected and the muscles reattached to the ischium. Sections showed: "Fragments of dense bone of a cancellous type and overproduction of hyaline cartilage and fibrous connective tissue. Calcification was present in all sections."

The patient was last seen in February 1968, 19 years after operation. He was free of pain and entirely asymptomatic. There was no limitation of his activity. X-ray films (Figure 1B) showed: "Asymmetry of the ischia; the right ischium has a sclerotic, 'scalloped' inferior margin. There are several small smooth ossific densities in the adjacent soft tissues."

Case 2. A 15-year-old boy was admitted to hospital in May 1961 because his family physician suspected bone tumor. A year before, patient had slipped while playing basketball and suddenly flexed his right hip in abduction. There was immediate pain and discomfort but no real impairment of his usual activities. He had mild discomfort when sitting. X-ray films at that time, February 1960 (Figure 2A) showed: "Avulsion of the apophysis and a portion of the adjacent margin of the right ischium with distal shift of this fragment of about 3 cm." The patient received no treatment then.

On examination at the time of admission, a hard fixed mass was felt in the posteromedial aspect of the right thigh, extending inferiorly from the ischial tuberosity about 6 cm. The gait was normal and there was no tenderness. The legs were of equal length and there was no muscle atrophy. Bilateral tightness of hamstrings was noted but the range of motion of the right hip was normal. X-ray films (Figure 2B) showed: "Extensive new-bone formation around the

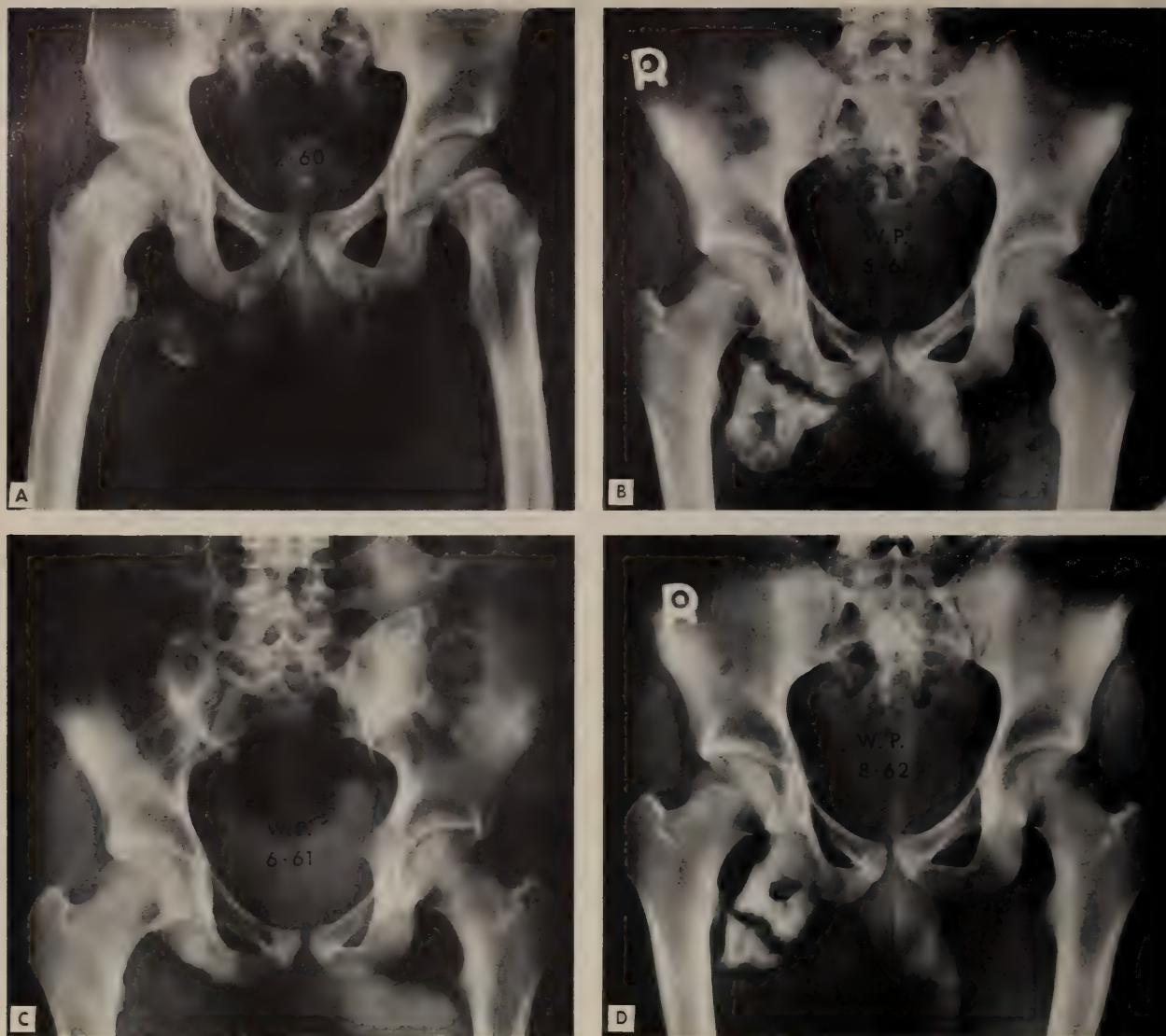


Figure 2 (Case 2).—A—Immediately after injury, showing avulsion of the apophysis and a portion of the adjacent margin of the right ischium with inferior shift of this fragment of about 3 cm. B—Fifteen months later extensive bony overgrowth is shown around the avulsed ischial apophysis with irregular ossification centrally. The patient was relatively asymptomatic. C—Film taken after operation shows residual faint calcification in the soft tissues. D—Film taken 14 months after operation shows regrowth and reossification of the bony mass. The patient, however, was asymptomatic.

avulsed ischial apophysis. There is an irregular ossified bony mass measuring 5 x 6 cm projecting inferolaterally from the ischium and separated from it by a 1.5 cm cleft. The apposing margins of the ischium and the apophysis are 'scalloped' and there are faint, irregular calcifications along this line."

The ischial apophysis was removed surgically, the ischium trimmed, and the hamstring muscles repaired. Sections showed osseous and cartilaginous tissue with areas of metaplasia. Periosteal new bone was present around the periphery of

the densely ossified matrix. Recovery was uneventful and films shortly after operation showed some soft-tissue calcification in the region of the removed mass. (Figure 2C.)

The patient was asymptomatic, but films taken 14 months after operation (Figure 2D) showed: "There has been regrowth and reossification of the mass noted in May 1961 and this is approximately the same size as on that examination. It is fused to the ischium, but there is a cleft across it at the junction of the middle and distal thirds with irregular calcification."

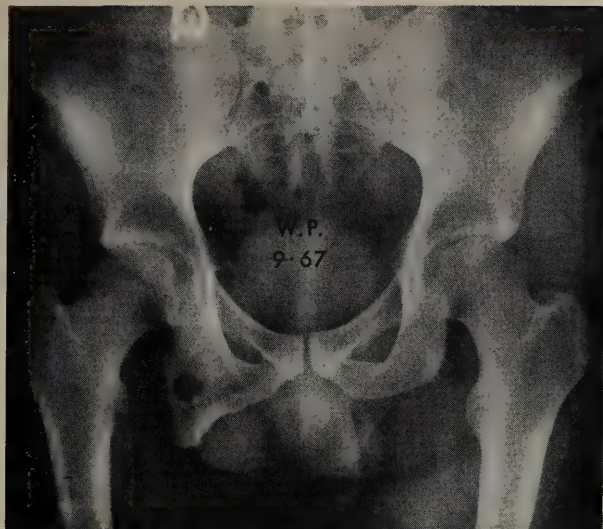


Figure 3 (Case 2).—Film six years after operation shows some involution of the bony mass, which extends 4 cm below the ischium. The patient was still asymptomatic.

There was some involution of the bony mass without additional treatment, and six years later films (Figure 3) showed that it extended 4 cm below the ischium. The patient was asymptomatic at this time and engaged in athletic events without difficulty.

Case 3. At age 13, the patient began to have pain in the left hip and buttock. There was no definite history of trauma, but he may have injured himself when getting out of a jeep rapidly six months earlier. Because of mild but constant pain x-ray study was done two years later. This showed (Figure 4A): "Old avulsion of the apophysis of the left ischium with slight separation and irregular calcification along the cleft. There is about 25 percent bony overgrowth of this center as compared with the right side. The margin of the left ischium shows an irregular, shallow defect."

Operation was not done; the patient was treated symptomatically. In the next seven years the pain decreased and when last seen at age 23, he was asymptomatic and engaged in sports without difficulty except for some discomfort when jumping hurdles. Films at this time showed (Figure 4B): "Residual deformity of the left ischium, which is widened and has a slightly irregular trabecular pattern, secondary to union of the previously noted avulsed apophyseal center."

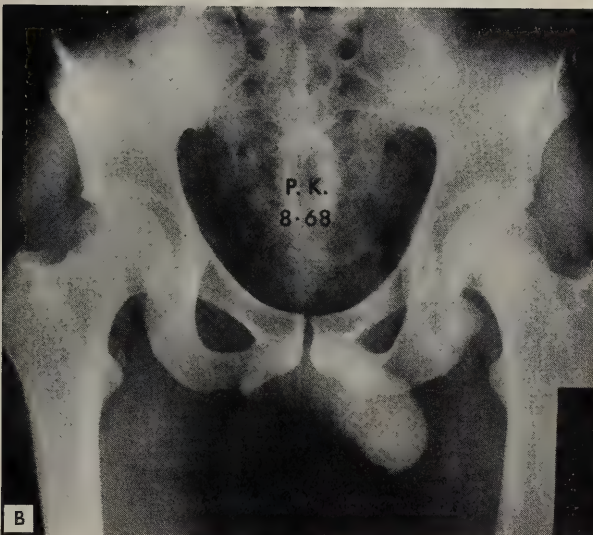
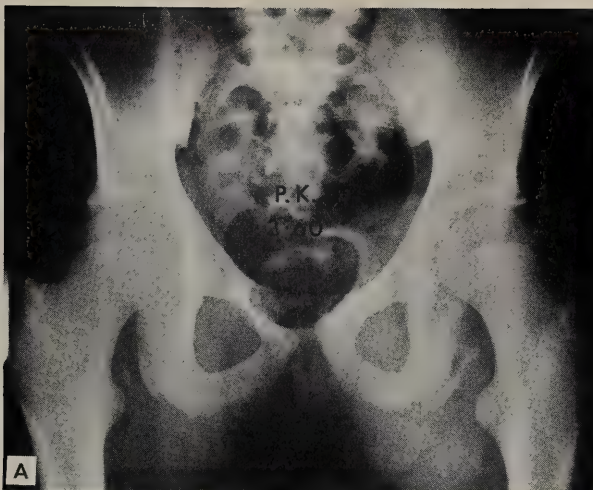


Figure 4 (Case 3).—A—Film taken two years after minor trauma shows avulsion and slight overgrowth of the apophysis of the left ischium. B—Deformity of the left ischium secondary to union of the old avulsed apophysis, ten years after trauma. The patient was asymptomatic.

Discussion

The treatment of this entity should depend on the extent of injury and the clinical findings. It is now well recognized that some cases of ischial apophyseal avulsion respond very well to conservative treatment, and follow-up reveals bony union of the apophysis with deformity but no symptoms. On the other hand, avulsion with pronounced separation of the fragments or avulsion of the center plus a fragment of ischium may call for more definitive treatment with surgical reduction. In late cases of bony overgrowth causing pain or impairment of activity, excision of the mass may be necessary. Before deciding

on treatment the problem in each case should be analyzed, with severity of initial symptoms, time elapsed between injury and the initial examination and the extent of the deformity shown by the radiograph all taken into account. It is our belief that in the presence of a fresh avulsion fracture with significant separation of the fragments, early open reduction is indicated.

Summary

Three cases of avulsion of the ischial tuberosity are presented. Two of these patients who had pronounced bony overgrowth, were referred because of suspicion of bone tumors.

Avulsion fractures, if there is no displacement, respond very well to conservative treatment. In avulsion fracture with separation of the fragments, early open reduction should be the treatment of choice. In old ununited cases, removal of the mass with reattachment of the tendons is indicated if the patient is symptomatic.

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Refer to: Davidson S: Solitary myeloma with peripheral polyneuropathy—Recovery after treatment. *Calif Med* 116:68-71, Jan 1972

Solitary Myeloma with Peripheral Polyneuropathy—Recovery after Treatment

SHERWOOD DAVIDSON, M.D., *Los Angeles*

PREVIOUS REPORTS have discussed the occurrence of peripheral neuropathy and myeloma. Chronic polyneuropathy associated with either multiple myeloma or solitary myeloma has been described.^{1,2,3}

Some recent papers have noted the neuropathy of myeloma as the presenting complaint and compared this syndrome with the neuropathic phenomena which occur as remote, non-metastatic complications of occult carcinoma.^{4,5}

Most of the patients described have had multiple myeloma but some had solitary myeloma.⁶ A particular relationship between an osteosclerotic type of myeloma and peripheral neuropathy has been suggested.^{7,8} Postmortem examinations have not revealed direct myelomatous or amyloid infiltration of the peripheral nerves but demyelination has been noted in the spinal cord, nerve roots and peripheral nerves.^{9,10}

The patients who present with occult solitary myeloma, manifested by only peripheral polyneuropathy, are a particularly interesting group, since many of them have normal sternal bone marrow and normal peripheral blood smear, and do not have abnormalities of serum protein immuno-electrophoresis or Bence-Jones proteinuria. The spinal fluid protein is often elevated. Roentgenograms of the skeleton usually reveal an osteolytic lesion or, less often, osteosclerosis.

The present case report is of particular interest because it provides an example of the diagnosis, treatment and recovery of a patient with a soli-

From the Department of Neurology, Southern California Permanente Medical Group, Los Angeles.

Submitted January 28, 1971.

Reprint requests to: S. Davidson, M.D., Department of Neurology, Southern California Permanente Medical Group, 4900 Sunset Boulevard, Los Angeles, Ca. 90027.

tary myeloma presenting as a symmetrical peripheral motor and sensory polyneuropathy of all extremities. Furthermore, there has been no evidence of recurrence of myeloma after surgical and radiation therapy of the lesion. After treatment there was almost complete recovery from the neuropathy and no recurrence during six and a half years of observation.

Report of a Case

A 62-year-old man, an office clerk, was seen in neurologic consultation in June 1965 with complaint of weakness and numbness of both feet and legs. He had first noticed numbness of both feet in December 1964, and it progressively ascended to the knees. Associated weakness of both feet made it impossible for him to walk or dance normally. He had experienced a mild upper respiratory illness at the time of onset of the leg symptoms. He said he did not drink alcoholic beverages and his diet apparently was normal. He had been treated for gonorrhea and syphilis about 30 years ago. A recent complete physical examination had revealed no significant findings.

Complete blood count, blood VDRL, urine analysis and lumbosacral spine roentgenograms were reported as normal. The two-hour postprandial blood sugar was 85 mg per 100 ml. Electromyography revealed pronounced fibrillation activity and positive sharp waves in the anterior tibial, peroneal and gastrocnemius muscles bilaterally. There was voluntary motor unit activity in all muscles tested. As there was no response to maximum stimulation of the right peroneal nerve, nerve conduction velocity could not be estimated. No other nerves were tested.

Neurologic examination at that time revealed marked weakness in flexion and extension of the toes and feet with impairment of position sense in the toes and poor vibratory sense as high as mid-leg bilaterally. Pinprick sensing was impaired bilaterally from the knees down. The tendon jerks were hypoactive everywhere. Both plantar responses were flexor.

A Schilling test, blood sedimentation rate, diagnex blue test and lupus erythematosus test were all normal. Urine determinations for lead, thallium, arsenic and mercury were within normal limits and the urine did not contain porphobilinogen.

Three weeks later the gait was more abnormal, with greater weakness in the lower extremities.



Figure 1.—A lateral view of the sacrum and coccyx; showing a scalloped erosion of the anterior margin of the inferior sacrum and the coccyx at the site of myeloma.

There was impaired sensing of vibration as far up as the iliac crests and of pinprick up to the knees. The patient complained of numbness and paresthesiae in the fingers of both hands at that time. When he was admitted to hospital a week later there was weakness in dorsiflexion of both hands, and the weakness of the legs had progressed to involve flexion and extension at the knees and hips.

The cerebrospinal fluid was clear and colorless, containing 56 mg of protein and 37 mg of sugar per 100 ml and 17 red blood cells and 4 mononuclear cells per cu mm. A Kolmer test was negative and the gamma globulin content was 14.6 percent. A skin and muscle biopsy of the left gastrocnemius revealed a slight increase of lymphocytes with no amyloid or other abnormalities seen. Liver biopsy was reported to show no pathologic changes. A bone marrow study showed thrombocytosis. Peripheral blood cell counts



Figure 2.—Appearance of the specimen of the tumor removed from the sacrum and coccyx. Hematoxylin-eosin stain $\times 100$.

were normal except for an increase in platelets. Results of serum protein electrophoresis was normal, as were determinations of serum calcium, phosphorus, and alkaline phosphatase. The urine was negative for Bence-Jones proteins.

Investigations for occult malignant disease led to suspicion of a pelvic mass but on abdominal exploration no abnormality was observed. A repeat series of bone roentgenograms revealed erosion of the left side and anterior aspect of the coccyx and lower sacrum (Figure 1), and a barium enema study showed an apparent anterior displacement of the rectum, consistent with the presence of a mass anterior to the sacrum.

A firm, well encapsulated, yellow tumor involving the lower two segments of the sacrum and the coccyx was removed in August (Figure 2). The pathologist reported the tumor was plasmacytoma. (The slides of the tumor and adjacent bone were reviewed by Dr. B. Q. Banker, Associate Professor of Pathology, Case-Western Reserve School of Medicine, Cleveland, who agreed with the diagnosis of myeloma.)

Following operation the site of the tumor was irradiated with 4200 r of cobalt 60 therapy. Within a week after operation the patient began to notice diminished numbness of the hands and feet, and over the following months he had progressive recovery of strength in all extremities. A year later there was only moderate weakness of dorsiflexion of the toes and feet, dysesthesia to pinprick over the distal one half of the legs, and slightly impaired vibration sense in the toes. At last report his strength had continued to improve and he was active physically. Barium

enema studies and roentgenograms of the spine, sacrum and coccyx have revealed no progressive changes. Twenty-four hour urine electrophoresis for Bence-Jones protein is negative. Serum protein immuno-electrophoresis is normal.

Discussion

Sensory and motor peripheral polyneuropathy is probably quite rare in myeloma; the incidence is lower than in association with distant carcinoma. Croft and Wilkinson¹¹ reported 15 cases in a group of 103 cases of carcinomatous neuropathy of all types, and Silverstein and Doniger² observed ten such cases in a series of 277 myeloma patients with neurologic complications of all kinds.

Spinal cord compression is the most frequently described neurologic complication of myeloma. In one review,² the incidence of the more common neurologic complications was: single nerve root compression and pain, 22 percent; compression of spinal cord and cauda equina, 10 percent; intracranial compression of cranial nerves, orbit and brain or brain stem, 2.5 percent.

Morley and Schwieger⁸ found reports of 23 cases of polyneuropathy with myeloma in the literature, and added four cases. Ten patients had single myelomas, one of whom (their Case 2) improved after radiotherapy.

The important features in the present case are the peripheral symmetrical motor and sensory neuropathy of all extremities, the solitary osteolytic myeloma, the absence of diagnostic changes in the serum and urine proteins and bone marrow, the pronounced improvement of the neuropathy following surgical and radiation therapy of the myeloma site, the long period of survival without evidence of recurrence of the myeloma with sustained improvement in the polyneuropathy, and the fact that there were no abnormalities of serum and urine proteins.

The peripheral neuropathy was similar to that reported with myeloma, having started in the lower extremities and affecting them more severely. There was no evidence of amyloid or myeloma infiltration in the biopsy specimen, and electromyography and motor conduction velocity tests in the legs were diagnostic of peripheral neuropathy. The fact that there was pronounced, sustained reduction of neuropathic impairment, with complete recovery in the arms and hands,

would indicate that a metabolic or auto-immune effect was active, rather than a direct infiltration or compression of the nerve roots or peripheral nerves by myeloma cells. The cobalt therapy directed to the coccyx and sacrum would not have reversed the effect of the myeloma deposits in the nerve roots or peripheral nerves at a distance from the site of the radiation therapy.

The survival is evidence to confirm the opinion of those who believe there is a syndrome of solitary myeloma, which, when treated locally by appropriate surgical operation and irradiation, has an excellent long-term prognosis for freedom from multiple recurrent myelomatosis.^{12,13} Usually in these cases there are no abnormalities of serum proteins, Bence-Jones protein, bone marrow or peripheral blood.

Summary

In the present case the patient recovered from peripheral polyneuropathy after removal of an occult solitary myeloma, with no recurrence of myeloma or neuropathy in more than six years of observation. This is particularly important since the solitary myelomas, as illustrated in this case, may be curable. The bone survey roentgenograms are particularly important in the

evaluation of patients with progressive neuropathy when the serum and urine protein, bone marrow and peripheral blood are normal and the other usual roentgenographic studies of the urinary, intestinal and respiratory systems are negative for occult carcinoma.

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IS MARIJUANA THE EDGE OF A WEDGE?

Does marijuana smoking lead to the use of other more dangerous drugs?

The answer is yes and no, which is not hedging. When you examine the statistics on heroin addicts, 80 to 90 percent of them have previously used marijuana. Ninety-five percent have also used alcohol, 100 percent have used mother's milk or some derivative or substitute; yet we don't implicate these things as causes of heroin addiction. If you like to quote authorities, you could always quote the President's Advisory Commission . . . which says that is no causal relationship between marijuana and heroin; I think that's true.

What is also true, though (particularly in young people) is that once the individual starts experimenting to alter his perceptual boundaries with one drug, he is often inclined to go to other drugs. Most young people won't go to heroin. Many now won't go to LSD. But often they will go to the "fruit salad" kind of drugs (the indiscriminate mixture of different types of pills). Particularly with the young people we see a great deal of this.

—J. THOMAS UNGERLEIDER, M.D., Los Angeles
Extracted from *Audio-Digest Pediatrics*, Vol. 16, No. 5, in the Audio-Digest Foundation's subscription series of tape-recorded programs. For subscription information: 1930 Wilshire Blvd., Suite 700, Los Angeles, Ca. 90057

Special Article

How Members Have Their Say in the AMA

ROBERT C. COMBS, M.D., *Irvine*

THE AUTHORITY FOR ESTABLISHING policy for the American Medical Association rests primarily in the hands of 244 physicians who constitute the AMA House of Delegates. State representation is based on one delegate per thousand AMA members or fraction thereof; each state has at least one delegate. In addition, there is one delegate each from the Veterans Administration; the Public Health Service; the medical departments of the Army, Navy and Air Force; and each of the scientific sections of the AMA (surgery, psychiatry, and so forth).

The House meets regularly twice a year: the Annual Session takes place in June and the Clinical Session usually begins the first weekend after Thanksgiving. Although these are the only formal meetings of the House of Delegates, the business of the House is carried on throughout the year. Commissions and standing and special committees are continuously engaged in investigative, planning, and reporting duties. They carry out the policies established at previous sessions and gather material for reports to be considered at forthcoming meetings. By this means, delegates to the House serve not just for the few days of the scheduled session but throughout the year.

Many delegates are officers of county or state medical societies or are active members of committees and commissions thereof. While performing their duties as such, sitting as members of their state house of delegates, or acting on behalf of their own county societies and hospital staffs,

delegates should be continuously alert to the expressed wishes of their colleagues, thereby gaining the knowledge necessary to represent them effectively when the AMA House of Delegates is in session. The members of the CMA would be well advised to know their 25 delegates and 25 alternates and to make their wishes known to them.

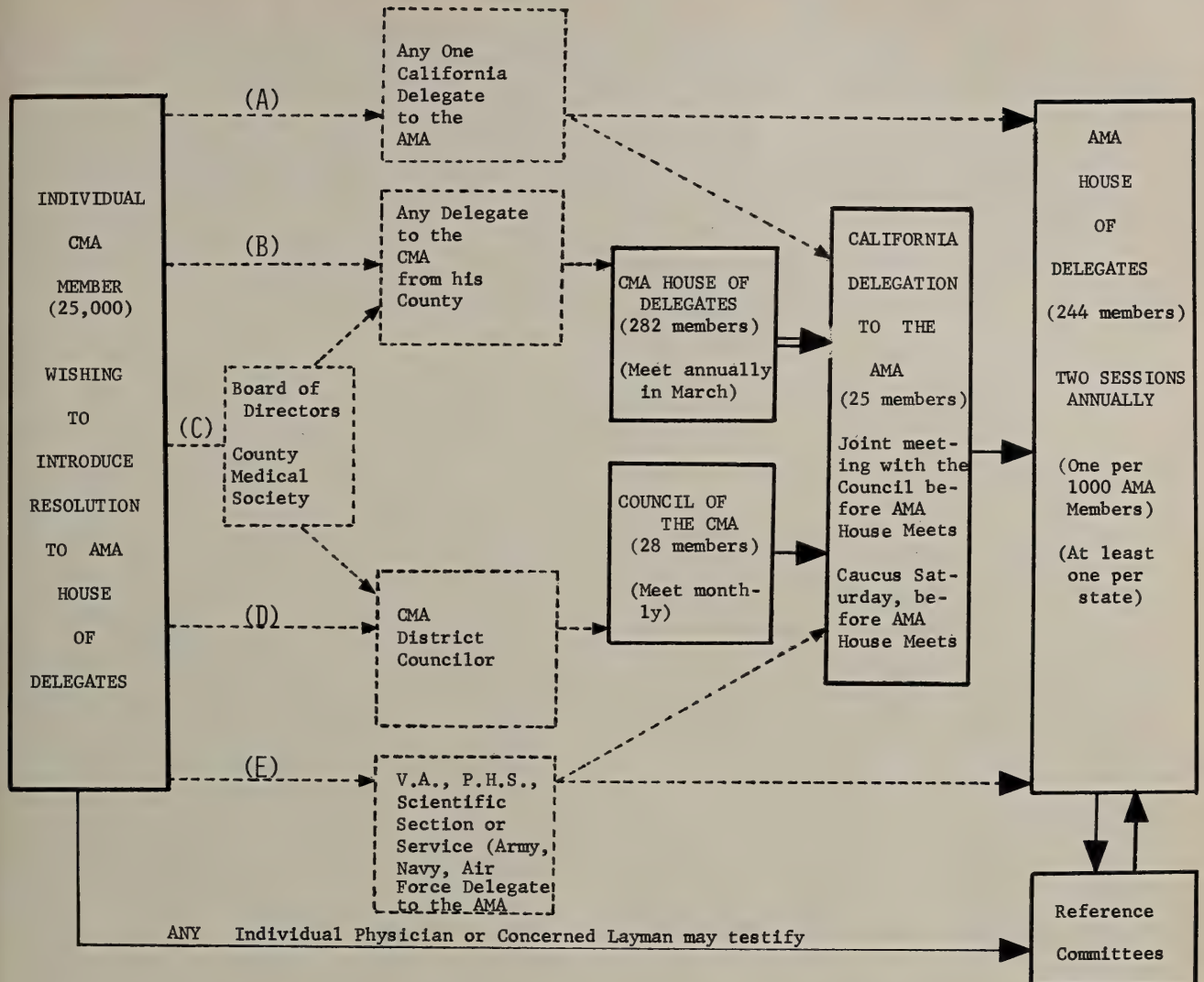
The accompanying diagram shows that it is relatively simple for any one of the 25,000 CMA members to have a concept dealing with medicine or medical care considered in the form of a resolution by the AMA House of Delegates. Some of the routes shown on the chart are most direct and simple, but there are also other approaches that are sometimes more effective in that as a measure progresses toward becoming the official business of the national parliamentary body it can gather the support of other individual physicians and of official bodies of the local and state medical societies.

In Approach A (see chart), if a California physician can convince one of the 25 delegates from California that his proposed resolution has merit, the delegate then can routinely introduce the resolution into the AMA House of Delegates at any time up to noon of the Saturday preceding the first meeting of the House. The delegate is not required to seek the support of the California delegation or even to bring the matter to its attention. Nor is it necessary that he himself subscribe to the proposition. If he does submit the resolution to his delegation for its consideration and can convince the delegation of the merits of the proposition, he will gain the support of the strongest delegation to the AMA.

Dr. Combs is Chairman of the CMA Delegation to the American Medical Association.

Reprint requests to: Division of Professional and Public Relations, California Medical Association, 693 Sutter Street, San Francisco, Ca. 94102.

HOW YOUR RESOLUTION REACHES THE AMA



Any resolution reaching the California delegation from whatever source is reproduced and mailed to all members of that delegation for their consideration. This action usually results in suggestions which materially strengthen the proposal. If introduced as a resolution of the California delegation, its chances for adoption at the national level are immeasurably increased.

At the last session of the CMA Council before the meeting of the AMA House of Delegates, a meeting of the Council and the California delegation is held to enable the delegates to learn the attitudes of the Council on the many resolutions. Although this meeting is usually attended by the entire delegation, the delegates may be represented only by the chairman of the delegation and the chairman of the Committee on Resolutions.

As indicated in Approach B, if time permits, it is advisable for the author of a resolution to submit it to the CMA House of Delegates through any delegate from his county society. Since the CMA House of Delegates meets only once annually (usually in March), a rather long lead time obviously is needed. On the other hand, this approach provides the benefit of discussion by the county delegation and, if the proposal is favorably considered by the CMA House, the support of that most significant body. Our AMA delegation believes that if the CMA House of Delegates instructs it to introduce a resolution to the AMA House, it must do so. On rare occasions the delegates may vote not to introduce a resolution because intervening events or new knowledge acquired after the receipt of the instructions make a change of course necessary, or

because they have learned that such a resolution would be contrary to the public law or other governing regulations. In such circumstances the delegation must be willing and able to explain to the CMA House of Delegates its reason for withholding the resolution.

Over the years we have observed that what becomes AMA policy today often had become the policy of one or several states two or three years previously and indeed had been first inaugurated at the county level in those states even before that. Hence the pathway indicated by Approach C should be considered fundamental. When the individual physician, through whatever techniques prevail in his county, brings an issue to the board of directors of his county medical society, it should receive that board's earnest consideration; and, if circumstances warrant, it should be directed onward either through a delegate from the county to the CMA House of Delegates or through the district member of the Council of the CMA. Many of the resolutions carried forward by the California delegation come from the Council. They may originate in the Council as a result of its deliberations, or they may have been brought to the Council by the district Councilor on the instructions of a county medical society. As depicted in Approach D, the individual physician may have personally approached the councilor from his own district. The strength of Approach C is that any resolution traversing this path has benefited from the combined thinking of individuals at all levels of organized medicine in California.

Issues which pertain primarily to the practice of medicine in the Veterans Administration, the Public Health Service, one of the armed services (Army, Navy or Air Force), or one of the specialty groups (such as urology, radiology or

pediatrics) are sometimes best introduced to the House of Delegates of the AMA through the representative of the special group. Just as in Approach A, this delegate can introduce the item directly to the AMA house. On the other hand, if the special delegate comes from California, he traditionally sits with our caucus and therefore would have submitted the resolution to us to inform us and solicit our support. Last year four of these special delegates were from our state, which in effect increased the size of the California delegation to 29.

The individual physician has not only a right to introduce a resolution by any of the above techniques but also a right to speak to any resolution before a reference committee of the AMA House. Most of the discussing, debating, and amending of resolutions takes place before the various reference committees. A member of the AMA needs no special permission to appear before these committees and can speak to any resolution under consideration, including his own. If he feels it wise to have interested laymen enter the discussion, with permission of the chairman of the committee they may have the privilege of the floor. If the individual supporter of a resolution is dissatisfied with the action of the reference committee, he can request and, with the support of two-thirds of the House of Delegates, be granted permission to argue the issue on the floor of the House. This course of action is rarely followed because along the way the resolution either will have gained the support of members of the House who will then champion it, or the sponsor, having heard the debate, will have surrendered. Nevertheless, the right is there, and to exercise it is entirely proper should the need arise.

It is your AMA. You can help to make its policy.

BLEEDING VARICES, GLABROUS CHEST?—CIRRHOSIS

Whenever I see a patient with bleeding varices who has no hair on his chest, that's cirrhosis of the liver until proven otherwise. . . . Well over 90 percent of cirrhotics have no hair on their chest.

—PHILIP THOREK, M.D., Chicago
Extracted from *Audio-Digest Surgery*, Vol. 17, No. 23, in the Audio-Digest Foundation's subscription series of tape-recorded programs. For subscription information: 1930 Wilshire Blvd., Suite 700, Los Angeles, Ca. 90057

In the Forefront

The San Fernando Valley Health Consortium

A Mustering of Community Resources for Health Manpower

GEORGE J. HOLLAND, PH.D., AND ADDIE L. KLOTZ, M.D., M.P.H.,
Granada Hills

THE SAN FERNANDO VALLEY IS A distinct geographic entity approximately 144 square miles surrounded by mountains on all sides. Although just minutes away from downtown Los Angeles by freeway, it is in many ways isolated and maintains its own character. We may look upon this valley, approximately ten miles wide and fourteen miles long, as a natural health education laboratory containing almost a million and a half inhabitants.

The San Fernando Valley's population growth has been phenomenal and is reflected in the student body growth at San Fernando Valley State College from less than a thousand in 1960 to over 23,000 at present. The past 50 years have seen the Valley evolve from ranch land, walnut and citrus groves to a bedroom community from which a majority commute daily to their jobs in Los Angeles.

The people who live in the San Fernando Valley include many affluent, who are concentrated particularly in the western and southern portions of the valley, as well as approximately a quarter of a million residents in what is known as the Northeast Valley who have an average income far below that of Los Angeles County or the State of California.

In 1969 a community health survey of the Northeast Valley was undertaken by the Northeast Valley Project of the California Regional

Medical Programs, Area IV (University of California at Los Angeles). That survey revealed the health needs of the Northeast Valley to be extensive. The need for health education of the citizens, 71 percent white, 20 percent brown and 9 percent black, was seen as the greatest need. Although health facilities seemed fairly adequate (before the 1971 earthquake), there were considerable problems in accessibility and utilization of those facilities, as well as acceptability. Approximately 15 percent had no health insurance of any kind.

An extreme shortage of health manpower was found to exist in the Northeast Valley. In some areas the physician-to-population ratio was as low as one to four thousand as compared with one to six hundred in other sections of Los Angeles County. Training opportunities for health professionals in the Northeast Valley were also extremely limited. Casa Loma College, in Pacoima, trains only about 100 allied health personnel a year. In that same area one in sixteen persons is employed in health related occupations, but the vast majority are frozen into low-level positions.

As the San Fernando Valley grew in population approximately twenty hospitals were established at various places in the valley in addition to two Veteran's Hospitals and the Olive View County Hospital; two junior colleges were formed and San Fernando Valley State College was designated a four-year institution. At present, however, the San Fernando Valley with its

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Reprint requests to: A. L. Klotz, M.D., San Fernando Valley Health Consortium, 10401 Balboa Boulevard, Granada Hills, Ca. 91344.

one and a half million inhabitants finds itself without a major medical training center. The ingredients are all present: faculty (many of the 1,200 physicians hold teaching appointments at University of Southern California or University of California at Los Angeles), clinical training facilities at the various public and private hospitals, educational institutions and potential trainees. What was needed was a catalytic agent to bring them all together. Thus, the San Fernando Valley Health Consortium was conceived in September 1969.

Representatives from San Fernando Valley State College began meeting with physicians, other health professionals and representatives from the indigent minority health planning group (Area IV RMP Northeast Valley Project). They informally explored the possibility of a joint endeavor by the community and the college in the education of allied health professionals and physicians in order to prepare for the needed changes in health care delivery in the San Fernando Valley. From these early discussions the San Fernando Valley Health Consortium concept developed. San Fernando Valley State College would serve as the umbrella of the Consortium with the primary responsibility for the academic aspects of the program. Community representatives, both professional and consumer, along with students, were to be intimately involved with both the organizational and curricular planning.

San Fernando Valley State College has a good academic base upon which to develop the Consortium, since fully accredited programs are already functioning in school and community health education, school nursing, physical therapy, environmental health, clinical laboratory technology, health statistics and dietetics. Master's level programs are available in many of those areas already. Curricula for medical records librarian, public health nursing, health administration and occupational therapy are proposed. The two junior colleges provide nursing, dental hygiene and other allied health professional training programs. Several of the high schools offer hospital occupations classes.

Through the Consortium, whose membership will comprise representatives from four areas (educational institutions, hospitals and health agencies, the various health professions and consumers), health manpower needs and resources

will be monitored longitudinally. Innovative training programs, opening the health career doors to high school students, will be developed. Articulation at all levels will be accomplished to provide lateral and upward career mobility. From a common core of courses applicable to all categories of allied health personnel, students could matriculate into upper division programs with great flexibility. In addition, the development of a core program will provide a mutual educational experience for those who are supposed to work together as health teams.

Lateral and upward mobility will be encouraged through transfer of credits and no one will be frozen into a particular dead-end channel, but can cross over and go on up the health career ladder. Granting of academic credit for work experience will also be cooperatively established among the various educational institutions.

Recruiting persons into academic areas, allowing them flexibility in moving up the academic ladder within a particular profession as well as laterally into related professions and returning them to their communities well equipped to cope with the health problems of an urban society—these are the Consortium's goals. Since none of the educational institutions in the San Fernando Valley Health Consortium has extensive, highly structured programs of long tradition, it is believed that much of the "academic vested interest obstruction" common in the development of inter-disciplinary programs will be minimal.

A registry of health professional students will be developed for the several San Fernando Valley training institutions so that a career lattice educational system can be effected. Professionals will be encouraged to move vertically, horizontally or diagonally up the career ladder through retraining, continuing education and academic-work equivalency programs organized through the Consortium. Hospitals and other institutions (including the health maintenance organization already in existence as the San Fernando Valley State College Student Health Service) will explore the need for the development of new allied health occupations to meet the needs of the rapidly changing health care delivery system. Experimental pilot retraining programs will be developed in areas such as clinical nursing practitioner, and neighborhood child health services specialists will be organized. A

medical education curriculum for primary physicians will eventually be developed and integrated into the core curriculum concept. Physicians' education must be drastically altered if we expect them to be able to work on professional health teams and to know how to utilize the various resources available to them.

The San Fernando Valley Health Consortium is not just a concept or an idea, it is an organizational reality. In 1970 planning monies were granted from Area IV and Area V of the California Regional Medical Programs. Addie L. Klotz, M.D., has been the College Director of the Consortium on a 20 percent time basis and George J. Holland, Ph.D., has been a half-time associate. In September 1970, an interim steering and planning committee, composed of health professionals, educators, hospital and health agency representatives, as well as a number of consumers, was organized and has been meeting monthly since that time. Eight task forces have been formed, again with representatives from those same four areas on each, to deal with the following areas of concern:

- Medical Education
- Legislative Liaison and Funding
- Review of Consortia Models and Determination of Program Priorities
- Survey of Existing Educational Institutions, Programs, Facilities and Personnel
- Survey of Health Manpower Needs
- Survey of Existing Community Health Facilities, Programs and Personnel
- Review of Curricular Models and Determination of Priorities
- Accreditation and Certification

These task forces have met and, as a result of the determination of priorities, articles of incorporation have already been formulated and approved by the interim steering and planning committee.

In all areas of concern, the concept of the San Fernando Valley Health Consortium has met with strong enthusiasm and support. Several local community hospitals have underlined their support with the actual donation to the Consortium of approximately five thousand dollars. Additional funding is being sought from many

sources, including National Urban Coalition, the Department of Health, Education and Welfare and various private foundations, and continued support is being sought from the Regional Medical Programs.

Because Area V Regional Medical Programs comprises areas outside the boundaries of the San Fernando Valley, and because Ventura County and the Antelope Valley are feeder areas for the San Fernando Valley State College, these areas will also be considered in further planning and organization.

Various professional organizations, including District 6 of the Los Angeles County Medical Association, have endorsed the concept of the Consortium and have offered assistance in its development. Great help has been given by Comprehensive Health Planning, Welfare Planning Council and other planning groups. Legislators, state and federal, have expressed interest and support.

In May a general orientation meeting was held on the State College campus and approximately a hundred persons attended. To this date, over two hundred have volunteered to serve on the various task forces. The interim steering and planning committee was set up as a self-destructing organization which would phase out once the San Fernando Valley Health Consortium Corporation became a working reality. The organizational structure of that body will consist of a board of directors representing health professionals, educational institutions, health care institutions and community consumers. There will be a college director responsible for academic aspects of the Consortium programs including accreditation review, curricular content and research and evaluation. A community director will also report directly to the board of directors. His job will include community health planning and training and overseeing the development of the Health Manpower Registry.

Because of the inherent resources already existing in the San Fernando Valley as well as its over-all youth and freedom from long-standing, inhibitory tradition, we see the success of the San Fernando Valley Health Consortium as a distinct and exciting possibility.

LETTERS *to the Editor*

More Physicians Through Perimeter Personnel Training

To the Editor: The editorial, "Medical Education in Transformation,"¹ inviting practicing physicians to participate, strikes a positive response. The areas in greatest need of medical care provision in which demand for services far outstrip the mechanics for production of medical manpower and facilities are the low economic and more remote geographic perimeter areas. The paraphrased adage, "a patient, an interested student, and an experienced doctor," names the essentials of fundamental medical education. Buildings, libraries, laboratories, and research programs are adjuncts in refinement for scientific advancement. Basic sciences and their application to medicine are the result of the efforts of doctors under duress who have utilized scientific method to construct fundamental developments in medicine.

People in isolated geographic or low income economic areas merit particular effort. This is an ideal locus for the development of multiphasic medical education-service projects. Physicians experienced in practice, young aspirants desirous of training for a medical professional career and medical educators may be coordinated for mutual advantage in medical care provision.

Improved services for patients in perimeter areas may be developed by and within the structure for a low cost service project, utilizing volunteers from the large body of undirected, bewildered, pre-medical school students who are rejected by the 108 medical schools in the United States. This group has increased from approximately 10,000 to 14,000 annually during the

last five years. According to Nicholson,² over 53 percent of the 26,000 total applicants this year were "non-accepted." The development of well planned training projects pointed toward challenging volunteers from this group to assist in the solution of the medical manpower crisis should be feasible in some measure in almost every area.

Recent JAMA articles and two editorials,^{2,3,4} deal with efforts of American students and to problems and the poor yield resulting from foreign medical school attendance.⁵

Continuing discussions at AMA, AAMC, and World Medical Association Assembly levels attest the need for action in this field by medicine and the seriously thoughtful public.

Admittedly, the non-accepted pre-medical students have lower grade-point and aptitude test averages than do the students admitted to medical schools. However, they are well above the college and university average and they have a demonstrable motivation for medicine.

The project proposed here for utilizing volunteers from this large reservoir of students offers an alternate route for the usual first academic year. This proposal combines two three-month concentrated training periods in the academic center separated by a nine-month supervised exposure to practical clinical experience at the community level. It goes like this: Early in the summer after non-acceptance, the volunteers would be screened by an interview team of an academic faculty member and an experienced clinician. This would be followed by a three-month orientation and technical training course comparable to that of the military medical corpsmen training. This should prepare the volunteer for the nine-month clinical experience as a "basic physician's assistant" actively contributing to patient care in areas of demonstrated medical service need under physician supervision. A second and final three-month clinically oriented biophysiological training in the medical center should be followed by comprehensive oral and written examinations.

Such a program should prepare the student and provide the faculty with a sufficient base for the selection of candidates from this group to be enrolled into the second year medical school class. Those students who have demonstrated less aptitude should be directed toward training as an "advanced physician's assistant" or accepting one of the medical technological traineeships.

To encourage "upward mobility" and "the ability to achieve" in this group, it should be emphasized that after one or more years in the supporting career role, candidates may again apply for re-examination for medical school matriculation.

This project outline presents a broad base which permits the evolution and continued advance in the practical education of the participating students, stimulation of the practicing physicians, and widened horizons of medical center staff participants. A concomitant medical service should assure provision for increased primary medical care for patients and future physicians for these communities.

Effectiveness of the project will depend upon the concentration of action and coordination of interest stimulated by the participants and from the public itself.

CARROLL B. ANDREWS, M.D.
Sonoma

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No Dearth of Opportunity

To the Editor: During a nine-month period, March-November 1970, the Office for Health Manpower and Continuing Education of the Dean of the School of Medicine, University of California, San Diego, recorded brochures received through the mail announcing formal pro-

grams of conferences on various aspects of medicine for post-graduate education.

In 275 days, 211 separate offerings were received. The distribution by months was as follows: March, 39; April, 37; May, 14; June, 15; July, 8; August, 9; September, 40; October, 20; and November, 29. The conferences were distributed geographically as follows: San Diego area, 12; elsewhere in California, 30; west of the Mississippi, 66; east of the Mississippi, 96; Canada, 4; Europe, Africa and the Pacific, 1 each. The conference length was distributed as follows: 1 day, 30; 2 days, 58; 3 days, 59; 4 days, 22; 5 days, 12; 6 days and longer, 10; 17 were non-consecutive. Total conference time was 635 days, not counting travel.

Of the topics offered, 80% were primarily clinical. The most popular subject was cardiology, with 36 entries, endocrinology and metabolism were represented by 13, surgery by 11, neurology 8, cancer 8, immunology-hematology 8, pulmonary 5, and pediatric 5. Among the non-clinical topics, the most common were environmental health with 8, biochemistry with 7 and laboratory animals with 5. Sex, in one or another combination, was mentioned in only 4. And 3 were extensive medical tours.

We tried to post the notices, but quickly ran out of bulletin-board space. Our capable secretary threw in her glove, which she seldom wears.

No conclusions or morals are drawn.

MICHAEL B. SHIMKIN, M.D.

*Formerly Associate Dean for Health Manpower
University of California, San Diego
School of Medicine*

Dermatologic Radiotherapy—R.I.P.

To the Editor: Doctor Epstein's article in the November 1971 issue, "Dermatologic Radiotherapy—R.I.P.," is an example of how the inappropriate use of statistical methods can provide misleading and confusing information. This article would better be titled "Acne Radiotherapy—R.I.P." If the purpose were to obtain the opinions of the nation's dermatologists on the use of ionizing radiation in the modern practice of dermatology then the questions should have been so formulated. By limiting the inquiry to

acne a built in skew-factor has been added which does the subject matter of the title a gross injustice.

This "tunnel-vision" view of dermatologic radiotherapy leaves untouched the many other skin diseases, dermatoses and tumors for which radiotherapy may be and often is used with good results. This is a vast subject and even vaster is the use of dermatologic radiotherapy in the treatment of malignant skin lesions. Only after adequate inquiry into attitudes and practices in these and related fields such as the use of grenz ray therapy for benign dermatoses can one draw any conclusions about the death or survival of dermatologic radiotherapy.

I join Doctor Epstein in decrying the lack of training which has become the vogue in many residency programs. Even sadder is the emergence of third parties in the form of malpractice insurance carriers as arbiters of medical decisions in the choice of therapies. I, too, am a victim of the "pulled plug syndrome" having opted to discontinue the use of grenz and x-ray therapy rather than pay thousands of additional

dollars in premiums to have available an infrequently used modality which was not paying even the fees to cover the annual premiums.

J. DAVID BRAYTON, M.D.
*Assistant Clinical Professor
Dermatology
L.A. County-USC Medical Center*



The Author Replies

I doubt if Dr. Brayton's criticisms are significant. The treatment of acne is the prime indication for the control of benign dermatoses with x-radiation. Grenz rays is an entirely different situation because of the softness of these rays. Its minor absorption eliminates most of the alleged hazards of x-radiation therapy—including leukemia, genetic damage, thyroid cancer, shortening of life, etc. This survey shows definitely that the interference in training in dermatologic radiotherapy dooms this modality.

ERVIN EPSTEIN, M.D.
Oakland

DRUGS FOR TACHYARRHYTHMIA IN PATIENTS WITH MYOCARDIAL INFARCTION

Lidocaine is best given as a bolus of 50 mg and then given as an infusion of 1 to 2 mg per minute. If you start lidocaine infusion in a patient with ventricular ectopic beats in the first 24 hours after myocardial infarction and arrhythmia recurs, it is worthwhile not to increase the infusion rate but rather to give another bolus. Increasing the infusion rate to 3, 4, or 5 mg per minute sometimes leads to drug toxicity without subduing the arrhythmia. . . .

Lidocaine is effective in about 80 percent of patients who have multiple ectopic beats. In the remaining 20 percent, it will fail. The drug of second choice, in my view, is procaine amide. To control recurrent ventricular arrhythmias, this agent should be given in doses of anywhere from 250 to 500 mg to as high as 1 gram every three hours. It's rapidly dissipated.

If procaine amide is not effective, if the patient has many ventricular ectopic beats and the rate is 60, sometimes by raising the rate to 70 or 80 with atropine, you'll find that lidocaine becomes very effective or it may not even be required.

—BERNARD LOWN, M.D., Boston
Extracted from *Audio-Digest Internal Medicine*, Vol. 18, No. 1, in the Audio-Digest Foundation's subscription series of tape-recorded programs. For subscription information: 1930 Wilshire Blvd., Suite 700, Los Angeles, Ca. 90057

Peripheral Venous Diseases

JESS R. YOUNG, M.D.

Material Supplied by the American
Heart Association

Varicose Veins

General Comments

The disorder of varicose veins is one of the most common affecting man. This condition is probably the result of a congenital weakness of the venous walls and the valves. The incidence is higher in women than in men. Obesity, pregnancy, prolonged standing, and thrombosis of the deep veins are important contributing factors.

The most common symptoms are those of aching, fullness, or fatigue on standing which is relieved by recumbency or by the wearing of an elastic stocking. It is important in the diagnosis to exclude other conditions such as tension fibrositis, water-retention syndrome, osteoarthritis, or a disk that may be causing symptoms in a patient with varicose veins, for even severe varicosities may be relatively symptomless.

Superficial thrombophlebitis and external hemorrhage are possible complications of varicosities. When severe varicose veins have been present for years, chronic stasis changes may appear, with pigmentation, fibrosis, dermatitis, and ulcerations.

The aim of medical therapy is chiefly to relieve symptoms and to try to prevent the progression

of varicose veins. All patients with varicosities should wear elastic stockings, exercise their legs, keep their weight at an ideal level, and, when possible, should sit with the affected leg elevated. They should avoid wearing tight clothing such as garters and panty girdles, and should avoid prolonged standing. It may be helpful to elevate the foot of the bed between 4 and 6 inches to decrease venous pressure while sleeping.

When varicosities are small and the patient wishes treatment for cosmetic reasons, injections of sclerosing solutions may be attempted. For more advanced varicosities, the patient either should wear elastic stockings or else should undergo surgical removal of the affected veins by ligation and stripping. Any varices not removed by these procedures subsequently may be injected with sclerosing solutions as an office procedure.

Superficial Thrombophlebitis

Thrombophlebitis in one of the superficial veins may be caused by trauma, intravenous injections, or may be associated with certain systemic diseases such as blood dyscrasias. Recurrent superficial phlebitis may be the first manifestation of thromboangiitis obliterans or of an occult malignancy, or may occur for no apparent reason.

Superficial phlebitis usually presents as a red, warm, painful, tender nodular area directly under the skin along the course of a vein. Edema is not present. The clot is adherent and is rarely the source of emboli.

Erythema nodosum may be quite difficult to differentiate from superficial phlebitis, and a biopsy may be necessary. Cellulitis should present no problem in differential diagnosis, for the process is more diffuse and there is no palpable cord along the course of the vein. Lymphangitis likewise should present no problem in diagnosis, for again no thrombosed vein is palpable and lymphangitis is associated with chills and a high fever.

Most patients with superficial phlebitis need nothing more than rest and elevation of the extremity and application of warm, moist packs for a few days. When the pain and inflammatory reaction are severe, phenylbutazone or oxyphenbutazone may be given for three or four days.

The author is from the Department of Peripheral Vascular Disease, The Cleveland Clinic Foundation.

When the phlebitis continues to extend despite treatment, anticoagulation therapy should be initiated.

Deep Thrombophlebitis

Deep thrombophlebitis is still one of the more common complications of major surgical operations, pregnancies, fractures or injuries of the lower extremity, or any serious illness that requires the patient to be confined to bed. The increased incidence with congestive heart failure, polycythemia, ulcerative colitis, and carcinomatosis is well known. In many instances, deep thrombophlebitis occurs for no known reason.

Early venous thrombosis may not be recognized clinically because of the absence of local or constitutional signs. The first indication of its presence may unfortunately be the occurrence of pulmonary embolism. However this asymptomatic bland type of venous thrombosis (phlebotrombosis) usually progresses to the more inflammatory state of thrombophlebitis which can be diagnosed clinically.

In the majority of patients the onset of deep phlebitis is gradual and mild, and the symptoms are often mistaken for rheumatism or muscle cramps. The discomfort is described as a dull ache in the calf or in the region of the thigh which is worse on standing, but relieved by recumbency.

The findings in deep phlebitis include edema, distended superficial veins, localized tenderness in the calf region or over the femoral vein, and the presence of Homans' sign with pain in the calf region on dorsiflexion of the foot with the knee in flexion. Usually, only minimal systemic reaction accompanies deep venous thrombosis. A low-grade fever, slight tachycardia, malaise, or a sense of apprehension may be present.

Various methods have been proposed to detect intravenous thrombi, including the use of radioisotopes, ultrasonic flow detection studies, and measurement of electrical impedance. Although these tests hold great promise, venography remains the most definitive method of study and should be done when the diagnosis is in doubt.

Because of the constant threat of pulmonary embolus, anticoagulant therapy with heparin

should be started as soon as venous thrombosis has been diagnosed. Heparin is injected intravenously in doses of 5,000 units every 4 to 6 hours, or subcutaneously in doses of 10,000 to 15,000 units every 12 hours. If the diagnosis is in doubt, heparin should be given prophylactically, unless contraindicated, until venography is performed and the issue is settled.

Ligation or clipping of the inferior vena cava is performed in the patient in whom heparin is contraindicated, and in the patient in whom pulmonary embolus develops while he is on anticoagulant therapy.

The patient with deep phlebitis should be kept in bed with his extremity elevated and, if arterial pulses are present, treated with warm, moist packs. After from 5 to 7 days, the tenderness usually subsides and the patient may begin to ambulate. Then, the dosage of heparin is tapered and stopped. When significant edema persists, a well-fitted elastic stocking should be worn until such time that edema no longer appears when the stocking is not worn.

Venous thrombectomy may be considered in massive venous thrombosis, particularly in young, otherwise healthy patients.

Preventive measures against thrombophlebitis include early ambulation after operation, routine wearing of light elastic stockings by patients confined to bed, elevation of the foot of the bed, close attention to fluid balance to prevent dehydration, encouragement of active and passive muscle exercises, and avoidance of tight abdominal dressings.

Chronic Venous Insufficiency

After deep phlebitis, the occluded vein usually becomes recanalized but the valves remain permanently damaged. If the patient does not properly care for his leg and wear a good elastic stocking to control edema, signs of chronic venous insufficiency may develop many months or years after the episode of thrombophlebitis. These changes include chronic edema, pigmentation, induration, and dermatitis. After slight trauma, ulcers develop which may be extremely difficult to heal.

If the patient is seen at a time when he has only edema and pigmentation, preventive measures should be advised to prevent the complications of dermatitis and ulcerations. He should sleep with the foot of his bed elevated on 4 to

6 inch blocks. He must wear a well-fitted elastic stocking when ambulatory. Exercise such as swimming, walking, or bicycling should be encouraged, and prolonged standing or sitting should be avoided. Women should not wear panty girdles or garters.

If a small clean ulceration is present, a modified Unna paste boot is applied to the leg and changed at seven-day to 14-day intervals depending on the progress of the patient. During this period, he can carry on normal activities as long as his occupation does not entail prolonged standing. Most ulcers will heal in from 4 to 12 weeks.

When the ulcer is badly infected with surrounding cellulitis, hospitalization may be necessary. The patient should be put to bed with the foot of the bed elevated, constant soaks applied to the extremity, and systemic antibiotics administered. When the ulcer is clean, the paste boot can be applied.

Very large ulcers will heal more rapidly and have a better chance of staying healed if a skin graft is used. It is important to do a wide excision and remove all the indurated area surrounding the ulcer.

Regardless of the method used in healing the ulcer, the patient must continue to wear elastic stockings and carry out the other prophylactic measures to avoid recurrence of the ulcer.

Selected Items from the FDA Drug Bulletin— October 1971

Methotrexate: Its Use in Psoriasis

Psoriasis has for ages challenged the physician's therapeutic resources. A recurrent disease, it is characterized by exacerbations and remissions which sometimes are difficult to control with conventional therapies.

Some cases of psoriasis which are severe, disabling and resistant to conventional therapy have been effectively treated with the anti-metabolite drug, methotrexate.

The Food and Drug Administration and the FDA's Advisory Committee on Dermatology have reviewed a series of clinical investigations and based on the recommendations of the Advisory Committee, the FDA has concluded that methotrexate is safe and effective for the treatment of certain cases of psoriasis.

The FDA-approved directions for use in these cases will soon be available from the manufacturer Lederle Laboratories, and should be reviewed carefully before the drug is used in the treatment of psoriasis.

The labeling of methotrexate restricts its use in psoriasis to severe, disabling, proven cases recalcitrant to more conservative treatment and makes the following recommendations:

- screening of patients by all appropriate parameters to exclude administration of methotrexate to pregnant women and to patients with preexisting renal, hepatic, or hematopoietic disease;

- screening of patients to disclose any pre-existing infections that might be activated by use of an immunosuppressive agent; and

- ensuring the availability of facilities for close medical and laboratory supervision of patients receiving the drug for psoriasis. Supervision should include complete blood count, urinalysis, serum creatinine, liver function studies, and liver biopsy, if indicated.

Methotrexate should be used only by physicians who are thoroughly familiar with the severe adverse effects, including deaths, associated with the use of anti-metabolite drugs. Deaths that have occurred during methotrexate treatment for psoriasis usually have been preceded by signs and symptoms of bone marrow aplasia (e.g., hemorrhagic enteritis). Patients should be fully informed of the risks involved and closely monitored. The drug should be discontinued promptly in the event of developing renal or hepatic toxicity.

Methotrexate has been marketed for 18 years as an important representative of anti-neoplastic chemotherapy. Use of an anti-neoplastic drug for treatment of an incurable dermatologic con-

dition must be carefully weighed by the physician after consideration of the risks and benefit to his patient.

Methotrexate should be used only when other less toxic drugs have failed to bring improvement to patients disabled with severe psoriasis. Please note that the drug is to be dispensed to patients *by physicians only*.

Spectinomycin for Acute Gonorrhea

FDA recently approved spectinomycin* for marketing. The drug is indicated only in the treatment of acute gonorrheal urethritis, proctitis, and cervicitis, when due to susceptible strains of *Neisseria gonorrhoeae*. This antibiotic, a product of *Streptomyces spectabilis*, is active against most strains of *N. gonorrhoeae* in a minimum inhibitory concentration varying between 7.5 and 20 mcg/ml. Cross resistance of *N. gonorrhoeae* between spectinomycin and penicillin has not been demonstrated.

Because of its high degree of efficacy and the long-term experience with penicillin, it is still considered the drug of choice for gonorrhea unless the organism is not sensitive to penicillin or the patient is allergic to penicillin. In addition, penicillin should be used when syphilis, suspected or confirmed, is concurrent with gonorrhea. Spectinomycin has no activity against syphilis. It should not be administered to children or during pregnancy.

Spectinomycin is administered only by intramuscular injection. It is rapidly absorbed. The antibiotic is not significantly bound to plasma protein. Spectinomycin can be administered safely to patients who are hypersensitive to penicillin.

For further details, including dosage, consult the package insert.

Drug Quality Control: Problem with Digoxin¹

In a recent monitoring program on digoxin tablets, the FDA's National Center for Drug Analysis reported that 47 percent of the batches investigated did not comply with the requirements of the USP monograph, chiefly because of failure in the content uniformity test. In one of

the worst examples, NCDA found digoxin tablets containing twice the declared quantity of active ingredients. The same bottle contained tablets with 60 to 70 percent of the declared quantity. The manufacturers agreed to recall the violative lots. A follow-up program on digoxin tablets is underway, and the Bureau of Drugs is monitoring production to assure content uniformity of individual tablets.

On the basis of the digoxin findings, and other studies of diverse pharmaceutical products containing high potency drug substances in relatively low concentrations, FDA has concluded that direct tests for content uniformity are essential. Testing of bulk formulation material has proved unreliable as a measure of uniform content in individual dosage units. When such procedure is used, it is still possible for many of the tablets punched from the formulation mass to fall far outside permissible potency limits.

The significance of this finding to the prescribing physician is obvious: If a previously well-digitalized patient displays signs of under- or over-digitalization, the problem may be with the drug rather than with the patient. Certainly, this possibility should be borne in mind when such signs appear.

The Food and Drug Administration is working to eliminate the problem of variable potency and its Bureau of Drugs has undertaken extensive investigations. In establishing the National Center for Drug Analysis, the Bureau has significantly expanded its capacity for gauging the quality of drug control in general. As a result of the Center's marked success in developing automated methods of analysis and applying them to individual units of dosage forms, NCDA is now able to focus attention on problem situations involving deviations from content uniformity requirements.

* "Trobicin," The Upjohn Company.

¹Adapted from a paper delivered at the Mid-Year Meeting of the National Association of Pharmaceutical Manufacturers, February 14, 1971, at Washington, D.C., by Daniel Banes, Ph.D., Director, Office of Pharmaceutical Research and Testing, Bureau of Drugs, FDA.

PUBLIC HEALTH REPORT

Frederick B. Hodges, M.D., Assistant Director, State Department of Public Health

Sudden Infant Death Syndrome (SIDS)

EACH YEAR, SOME 800 CALIFORNIA infants under one year of age, most of them appearing to be in good health, are put to bed by their parents at night and unexpectedly are found dead in the morning. A variety of names have been used to describe this situation, but *Sudden Infant Death Syndrome* (SIDS) seems to be best. The following definition of SIDS proposed at the Second International Conference on causes of SIDS has been adopted by the State Department of Public Health: "When death occurs in an apparently normal infant (age one week to one year) who died unexpectedly and suddenly, with lack of physical or autopsy evidence to adequately explain the death, the diagnosis 'Sudden Infant Death Syndrome' should be used on the death certificate and coded under I.C.D.A. code (8th edition), 795 Sudden Death (cause unknown)."

At the beginning of this same conference Dr. A. B. Bergman said, "It is now possible to say that Sudden Infant Death Syndrome is a real disease, not a vague mysterious killer." It is clear that there is a basic pathological mechanism responsible for the vast majority of these deaths, even though at present we cannot describe it in detail. It should be emphasized that efforts must be made, including detailed autopsy and indicated laboratory studies, to determine the cause

of death. If in the opinion of the coroner or pathologist a reasonable explanation for the sudden death can be made, the death should be ascribed to that particular cause and the appropriate I.C.D.A. code used. Only where the findings fail to provide a sufficient explanation would the death be attributed to SIDS.

A typical history reveals the victim to be an infant between the ages *two and four months* (90 percent between one and nine months, average age 2.8 months) who had been *previously in good health*, who may have had *minimal minor respiratory symptoms* immediately preceding, but who was put to sleep in the usual manner and was found dead in half of the cases *between midnight and 6 a.m.* There is an increased chance that this "typical" infant is male (60 percent) and comes from a socioeconomically disadvantaged family, from a premature or multiple birth, or from a Negro family and that the mother was younger than the average.

Of the infants who die unexpectedly, 15 to 44 percent show pathological findings which adequately explain the death and allow the death to be assigned to a specific cause. Definite and unequivocal findings which could produce death are lacking in the remaining cases. In 85 to 90 percent of these infants who die unexpectedly, and for whom the cause of death is not clear, there are some specific and predictable autopsy findings such as pulmonary and pharyngeal edema and petechial hemorrhages sharply limited to the thoracic contents. This combination of lack of specific cause and minimal but consistent findings on autopsy is the essence of the operational definition of SIDS.

Many theories as to the exact mechanism and cause of SIDS have been proposed: mechanical suffocation, hypersensitivity to cow's milk, deficient levels of immunoglobulins, parathyroid defi-

ciency, spinal injury, adrenocortical insufficiency, bacterial or viral infection and toxic agents. Careful evaluation has failed to establish any of these as significant causal factors.

It is suggested by Dr. Edward Shaw that since 30 percent of infants are obligate nose breathers with already narrow nasal passages, they are at risk of suffocation when there is further airway narrowing due to inflammation during a mild respiratory infection.

Neurophysiological studies show that during normal sleep small infants can be apneic 5 to 10 percent of the time. During a virus infection these spells may increase to 25 to 30 percent of the time. Also, it has been shown that the reactivity of the autonomic nervous system varies. Maturation seems to be reached around 2 to 3 months of age, so that normal protective automatic mechanisms may not be fully developed until after that time. The immediate cause of death in SMS is probably laryngospasm. Normal developmental changes occurring in the early months postnatally within the bundle of His and the A-V node may cause fatal arrhythmias under certain otherwise innocuous conditions.

It is probable that there is no single event that

triggers the pathological mechanism but that one or a series of conditions or events lead up to this final common pathway.

The puzzle of SMS is far from solved and the solution has been too long neglected. A first step is the collection of epidemiological data to provide clues for clinical research. For this reason the Department believes that SMS is a definite entity with a common pathological mechanism and should be officially so named.

1. When unexpected death occurs in infancy for which *definite* and *unequivocal* pathological findings sufficient to account for the death of the infant are missing, the diagnosis of SMS should be made.

2. In most cases, in addition to the history there are specific and recognizable pathological findings which although in themselves are not sufficient to result in death aid in assigning the case to SMS.

3. When applicable, the diagnosis SMS should be placed on the death certificate as the cause of death and uniformly coded.

These steps should be a major contribution in more clearly understanding this disease so that any possible preventive measures can be taken.

INCLUSION BLENORRHEA IN THE NEWBORN

There is one venereal disease that isn't usually considered in the newborn and that's inclusion blenorria. The virus that causes inclusion blenorria is an interesting agent. It sits in the cervix of the mother; it seems to be transmitted by a venereal route. The baby acquires the infection during the birth process. Then after an incubation period of five to 10 days, sometimes up to two weeks, he begins to develop rather runny eyes (usually on one side, spreading to the other) and then a profuse and purulent material. It's a relatively harmless disease except for the fact that the baby will have a purulent conjunctivitis for a period of perhaps several months unless it is treated. The treatment is tetracycline ointment, applied for a period of about 10 days. It's a rather slow response, but the condition does respond to tetracycline. . . .

Inclusion blenorria is a very easy disease to diagnose. You do some scraping from the lower lid conjunctiva and then stain the material collected. You can see the inclusion bodies in the conjunctival epithelial cells. This is a venereal disease, fortunately a relatively harmless one.

—HEINZ F. EICHENWALD, M.D., Dallas
Extracted from *Audio-Digest Pediatrics*, Vol. 16, No. 9, in the Audio-Digest Foundation's subscription series of tape-recorded programs. For subscription information: 1930 Wilshire Blvd., Suite 700, Los Angeles, Ca. 90057

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ation for **HOTEL ACCOMMODATIONS**
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CALIFORNIA MEDICAL ASSOCIATION

And

First Invitational Western States

Scientific Assembly

FEBRUARY 12-16, 1972

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SCIENTIFIC SESSIONS BEGIN SATURDAY MORNING, FEBRUARY 12

HOUSE OF DELEGATES OPENING SESSION SATURDAY AFTERNOON, FEBRUARY 12

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In Memoriam

Persons wishing to do so may make contributions to the Physicians' Benevolence Fund to honor the memory of a member who has died. Members of the family will be notified that such a contribution has been made and the name of the donor will be supplied.

Checks should be addressed to Physicians' Benevolence Fund, Inc., California Medical Association, 693 Sutter Street, San Francisco, Ca. 94102.

BRIEN, JACQUES G., Inglewood. Died October 24, 1971 in Los Angeles, aged 49. Graduate of University of Montreal Faculty of Medicine, 1951. Licensed in California in 1957. Doctor Brien was a member of the Los Angeles County Medical Association.

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BROCKWAY, ALVIA, Los Angeles. Died November 8, 1971 in Los Angeles of cancer of pancreas, aged 77. Graduate of Rush Medical College, Chicago, 1922. Licensed in California in 1922. Doctor Brockway was a member of the Los Angeles County Medical Association.

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BRODY, YALE, Stockton. Died September 8, 1971 in Stockton, aged 59. Graduate of Dalhousie University Faculty of Medicine, Halifax, 1934. Licensed in California in 1937. Doctor Brody was an associate member of the San Joaquin County Medical Society.

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BYINGTON, PRESTON CHINNOCK, Modesto. Died August 4, 1971, aged 79, of malignant lymphoma. Graduate of College of Medical Evangelists, Loma Linda—Los Angeles, 1924. Licensed in California in 1924. Doctor Byington was a member of the Stanislaus County Medical Society.

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CITRON, JESSE WILLIAM, Fremont. Died November 11, 1971 in Fremont of ventricular rupture, aged 84. Graduate of College of Physicians and Surgeons, Medical Department, University of Southern California, 1921. Doctor Citron was a member of the Alameda-Contra Costa Medical Association, a life member of the California Medical Association, and a member of the American Medical Association.

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COOK, EUGENE LEE, Torrance. Died October 13, 1971, aged 54. Graduate of University of Michigan Medical School, Ann Arbor, 1941. Licensed in California in 1945. Doctor Cook was a member of the Los Angeles County Medical Association.

COUCH, MANFRED RICHARD, South Pasadena. Died November 3, 1971 in San Marino of arteriosclerotic cardiovascular disease, aged 61. Graduate of Hahnemann Medical College and Hospital of Philadelphia, 1941. Licensed in California in 1946. Doctor Couch was a member of the Los Angeles County Medical Association.

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DALTON, MARK ARDATH, Long Beach. Died November 10, 1971 in Long Beach of acute cardiovascular collapse, aged 74. Graduate of Columbia University College of Physicians and Surgeons, New York, 1925. Licensed in California in 1928. Doctor Dalton was a member of the Los Angeles County Medical Association.

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KITCHEN, BURTON E., Eureka. Died November 13, 1971 in Eureka of heart disease, aged 58. Graduate of Washington University School of Medicine, St. Louis, 1940. Licensed in California in 1941. Doctor Kitchen was a member of the Humboldt-Del Norte County Medical Society.

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LEVSON, DANIEL N., San Jose. Died November 8, 1971 in San Jose, aged 39. Graduate of University of Manitoba Faculty of Medicine, Winnipeg, 1959. Licensed in California in 1967. Doctor Levson was a member of the Santa Clara County Medical Society.

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MACK, ERNEST A., Anaheim. Died July 15, 1971 in Anaheim of coronary artery thrombosis, aged 42. Graduate of University of Southern California School of Medicine, Los Angeles, 1958. Licensed in California in 1959. Doctor Mack was a member of the Orange County Medical Association.

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MEYERS, EDITH MARY, Alameda. Died November 12, 1971, in Alameda, aged 71. Graduate of University of California Medical School, Berkeley—San Francisco, 1926. Licensed in California in 1926. Doctor Meyers was an honorary member of the Alameda-Contra Costa Medical Association.

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MILLER, HELEN M. (KOKÉ), Oakland. Died November 8, 1971 in Oakland of adenocarcinoma of the uterus, aged 78. Graduate of University of Michigan Medical School, Ann Arbor, 1927. Licensed in California in 1943. Doctor Miller was a retired member of the Alameda-Contra Costa Medical Association and the California Medical Association, and an associate member of the American Medical Association.

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MOLONY, WILLIAM RUDOLPH, JR., Los Angeles. Died November 14, 1971 in Los Angeles of injuries received when struck by an automobile, aged 68. Graduate of

St. Louis University School of Medicine, 1927. Licensed in California in 1927. Doctor Molony was a member of the Los Angeles County Medical Association.

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NIDER, GERALD KNOWLTON, Fresno. Died November 12, 1971 in Fresno, aged 76. Graduate of College of Physicians and Surgeons, Medical Department, University of Southern California, 1921. Licensed in California in 1922. Doctor Nider was a retired member of the Fresno County Medical Society and the California Medical Association, and an associate member of the American Medical Association.

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OLSEN, JOSEPH, Oakland. Died November 1, 1971, aged 63. Graduate of University of California Medical School, Berkeley-San Francisco, 1935. Licensed in California in 1935. Doctor Olsen was a member of the Alameda-Contra Costa Medical Association.

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SCHAUB, RICHARD A., Pasadena. Died October 30, 1971 in Pasadena of myocardial infarction, aged 74. Graduate of College of Osteopathic Physicians and Surgeons, Los Angeles, 1922. Licensed in California in 1923. M.D. degree from California College of Medicine, 1962. Doctor Schaub was a member of the Los Angeles County Medical Association.

SMITH, RALPH THADDEUS, Pomona. Died October 25, 1971 in Pomona, aged 99. Graduate of Rush Medical College, Chicago, 1900. Licensed in California in 1915. Doctor Smith was a member of the Los Angeles County Medical Association.

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STOREY, CLIFFORD F., San Diego. Died November 14, 1971 in San Diego, aged 66. Graduate of Tulane University School of Medicine, New Orleans, 1930. Licensed in California in 1955. Doctor Storey was a member of the San Diego County Medical Society.

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VARGAS, ROGER AGUSTO, San Bernardino. Died November 12, 1971 in San Bernardino, aged 68. Graduate of Loyola University School of Medicine, Chicago, 1934. Licensed in California in 1935. Doctor Vargas was a retired member of the San Bernardino County Medical Society and the California Medical Association, and an associate member of the American Medical Association.

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WALSH, ALTON L., San Jose. Died November 15, 1971 in San Jose of heart disease, aged 60. Graduate of St. Louis University School of Medicine, 1940. Licensed in California in 1948. Doctor Walsh was a member of the Santa Clara County Medical Society.

BOOK REVIEWS

CALIFORNIA MEDICINE does not review all books sent to it by the publishers. A list of new books received is carried in the Advertising Section.

GREEK MEDICINE IN ASIA AND OTHER ESSAYS—Major General S. L. Bhatia, CIE, MC., MA., MD. (Cantab.) FRCP (Lond.), FRS (E), FASC., Indian Medical Service (Retired). With a Foreword by H. E. Shri V. V. Giri, President of India, Indian Institute of World Culture, 6, B. P. Wadia Road, Basavangudi, Bangalore-4, India, 1970. 226 pages, no price in dollars listed.

It is fortunate that the author of this volume was widely recognized in his country as an outstanding physician and medical scientist and that he was elected to many important posts in the medical and scientific societies of India, for most of the essays included in this book are special lectures or presidential addresses to these societies. Fortunately, in spite of their disparate conception and delivery, the twelve individual essays form a harmonious whole and disclose the author as an erudite and scholarly physician. It is obvious that Dr. Bhatia's favorite avocation was the study of medical history of India and the Western World, for each of the essays reflects traces of a serious preoccupation with the evolution of medicine in India and its traces and connections with medicine in the West. As was to be expected, the first essay on "Greek Medicine in Asia" is by far the most important and far-reaching of his various studies.

The medical system based on Greek medicine is known in India as *Unani* medicine, and in the introductory chapter Dr. Bhatia confirms his familiarity with the evolution of Greek medicine by tracing its initial arrival in India to the armies of Alexander the Great in the third century B.C. On later occasions, and after the spread of the Moslem religion, other waves of Greek learning brought further knowledge of Greek medicine into India and was much revered. While these statements are entirely correct, it is worth noticing that Dr. Bhatia tends to fall victim to the Asian practice of priorism which induces him to state that the Indian physicians, Charaka and Sushruta, had preceded Hippocrates by several centuries in dissociating medicine from theology and magic. Whether this precedence of Charaka and Sushruta over Hippocrates was a historical fact can neither be confirmed nor denied, because early Indian history is almost wholly devoid of reliable chronicity.

But regardless of this and other somewhat chauvinistic statements, Dr. Bhatia's book is pleasantly informative and quite convincing in content. It also reflects the serious preoccupation of Indian physicians with the importance of their own medical history, and its debt to Western inspiration. It is to be hoped that The Indian Institute of World Culture which has espoused many praiseworthy causes will succeed in a worldwide dissemination of this important volume.

ILZA VEITH, PH.D.

THE ARTERIAL ANATOMY OF THE KIDNEY—F. T. Graves, M.S., F.R.C.S. The Williams and Wilkins Company, 428 E. Preston St., Baltimore, Md. (21202), 1971. 101 pages, \$13.00.

This delightful little red book describes the author's original study of the arteries of the kidney and their sig-

nificance in surgery. The style is relaxed (Chapter One begins, "It was a hot summer's afternoon in 1952. A bluebottle buzzed intermittently outside the theatre window. . .") yet clearly descriptive. The illustrations are excellent, and include many in full color depicting specimens injected to make multicolored arterial casts. Finally, the application of the author's findings to actual operations on the kidney is so clearly described and illustrated that the urologic surgeon can make good use of them.

FRANK HENMAN, JR., M.D.

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COMMON SKIN DISEASES—Diagnosis and Treatment—2nd Ed.—Howard T. Behrman, M.D., Professor of Clinical Dermatology and Director of Dermatologic Research, New York Medical College; Theodore A. Labow, M.D., Instructor in Dermatology, College of Physicians & Surgeons, Columbia University; Jack H. Rozen, M.D., Assistant in Dermatology, College of Physicians & Surgeons, Columbia University. Grune & Stratton, Inc., 757 Third Ave., New York City (10017), 1971. 189 pages, \$15.00.

This text is the second edition of an original publication in 1965. The original title, *The Practitioner's Illustrated Dermatology*, would seem more appropriate than the title of the second edition, *Common Skin Diseases: Diagnosis and Treatment*. This text is primarily an illustrated tour through the common entities in dermatologic practice. The pictorial content is all in color and excellently done. The photographs occupy about half of the space in the text and are cleverly arranged on one side of the page opposite to the clinical description and suggested therapy for the disease in question. On the surface, this would seem to be an excellent way to identify common skin diseases and thereby make a diagnosis on a given patient in the office. However, it is, in fact, not so simple and one might seriously question whether such a text does more harm than good as far as the practitioner's management of dermatologic disease is concerned. The format would be helpful to one unsophisticated in dermatology, if he had no access to a specialist in the field. This would also be a useful and pleasantly simple text for the beginning student in dermatology. There is a section at the end of the book concerning principles of treatment and specific agents to be used in topical therapy as well as internal medications for control of dermatologic disease. Again, there are gross oversimplifications but it contains useful orientation for the uninitiated.

RICHARD B. STOUGHTON, M.D.

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THE INTERVERTEBRAL DISC—Anthony F. DePalma, M.D., Professor of Orthopedic Surgery, Jefferson Medical College, Thomas Jefferson University; and Richard H. Rothman, M.D., Ph.D., Associate Professor of Orthopedic Surgery, Jefferson Medical College. W. B. Saunders Company, West Washington Square, Philadelphia, Pa. (19105), 1970. 373 pages, \$16.50.

"No operation in any field of surgery leaves in its wake more human wreckage than surgery on lumbar discs." By this statement the authors of this quite excellent and reasonably current text reveal their broad personal experience

with, and their humane attitude toward this common, recurring and disabling public health problem. In the 16 chapters, each with its own bibliography, the traditional approach to exposition is utilized with a nice balance and weighting of anatomical, pathological and clinical knowledge. This reviewer appreciates the even-handed presentation of unresolved or controversial features and the authors' willingness to commit themselves to a particular view or not depending upon the adequacy of knowledge upon which to base an opinion. The physical forces playing upon the intervertebral discs are helpfully discussed as are the biochemical and pathological changes in evolution of disease. The sections on clinical analysis are sagely presented and well and accurately illustrated, as are the chapters upon management, both conservative and operative.

One might disagree with the authors' eschewing the widespread use of myelography; one could note the lack of reference to the value of gas myelography or other refinements in correlations between functional anatomy and radiological assessment. One might disagree with the favored position accorded laminectomy for thoracic disc herniation or the authors' preference for combined excision-fusion procedures for lumbar herniations. These, however, represent a reviewer's differences from the authors' opinions which surely have been honestly reached by what appears to be a careful, intelligent analysis of their 20 years of focus on the problems of intervertebral disc disease. The sections dealing with the problems of patients having undergone multiple spine procedures are especially insightful and cogent.

This book, while not encyclopedic, is certainly the best of its kind on the market today. It is well produced, easily read, unambiguous and deserves reading by all who treat the various manifestations of disc disease, back and neck pain, et cetera. It is not a neuroscientist's reference, but it is a text worthy of students and generalists and should be mandatory for those who are in neurosurgical and orthopedic training.

W. EUGENE STERN, M.D.

* * *

HEMATOLOGIC PROBLEMS IN SURGERY—Harold Laufman, M.D., Ph.D., Director, Institute for Surgical Studies; Attending Surgeon, Montefiore Hospital and Medical Center; Professor of Surgery, Albert Einstein College of Medicine, New York; and Robert B. Erichson, M.D., Adjunct Attending Physician, Department of Medicine (Hematology), Montefiore Hospital and Medical Center; Hematologist, St. Joseph's Hospital and Hematologist, Laboratory Division, Stamford Hospital, Stamford, Connecticut. W. B. Saunders Company, West Washington Square, Philadelphia, Pa. (19105), 1970. 249 pages, \$10.00.

Although by outward appearances a concise well organized compendium of the hematologic problems faced by surgeons, the contents are sadly disappointing. There is no uniform quality to the book and the sections vary tremendously from pragmatic to irrelevant. The problem of thrombophlebitis and the postphlebotic syndrome is treated in great detail though its hematologic significance remains somewhat clouded. Careful instructions are given right down to the proper wrapping of the leg, step by step, with elastic bandages. On the other hand, in the sections on anemias, references are made to iron, B-12 and folic acid therapy, without mention of doses or treatment regimens. Although a lot of very valuable material is presented in a concise outlined form, the impact is diluted by many seeming errors or poorly explained statements, such as, "When iron is reduced in the body, absorption of iron decreases." A number of points are reiterated which are seemingly redundant to the average surgeon, such as for a patient with a history of bleeding,

adequate amounts of blood should be available for transfusion during the operation to counteract the possibility of operative blood loss.

Many statements will confound or confuse the unwary. Statements such as, "Almost no surgeons employ heparin in the postoperative period following these procedures" when referring to peripheral arterial surgical operations, are simply not justified.

In conclusion, one is forced to say that the book falls far short of its purported goals, though it does provide a neat little handbook if one's demands are not too great.

HERBERT I. MACHLEDER, M.D.

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HANDBOOK OF DRUG INTERACTIONS—Gerald Swidler. Wiley-Interscience—A Division of John Wiley & Sons, Inc., 605 Third Avenue, New York, N.Y. (10016), 1971. 384 pages, \$15.00.

The past several years have seen a striking increase in the awareness by physicians of the consequences of drug interactions. This awareness has been expressed in an increasing number of publications devoted to this area of therapeutics. Predictably, compilations of such interactions have begun to appear. The *Handbook of Drug Interactions*, by Gerald Swidler, was prepared because of the author's belief that, "there was a need by the physician and pharmacist for additional help in the safe treatment of patients . . . especially when more than one drug for the patient must be prescribed." One can only concur in that belief. However, I do not feel that the author has satisfied that need with his present effort.

The book suffers from several defects. Perhaps the most important of these is the limited and uncritical use of reference material. It would appear that the primary sources of information are package inserts and other literature provided by the drug manufacturers. These are quoted directly, and without qualification. An equally important defect is the inadequate presentation of the mechanisms of drug interactions. The author claims to have limited discussions of mechanism, since "many of them are so pharmacologically or physiologically complex that I felt I would be doing the reader a disservice by trying to condense this information . . ." In fact, the disservice results as a consequence of misleading conclusions which could be drawn from such incomplete discussions. Since the interactions between drugs are indeed complex, it is especially important that their mechanisms be clearly defined, when known. This definition will allow for the generalization of information to other agents of similar chemical or physical characteristics, and provide the basis for recognition of interactions through understanding rather than rote. Additionally, it is only through the understanding of the mechanisms underlying drug reactions that appropriate corrective measures can be undertaken. Again, the extremely limited use of primary source references makes it difficult for the interested reader to satisfy these deficiencies independently.

Finally, I found the cross-indexing unsatisfying in that most agents were referred to only by trade name. In most circumstances, the generic name of the agent was not provided, nor was there a reference to the class of the agent. The result of this is to further limit the reader's ability to generalize the information provided and allows only for drug-by-drug memorization, an inefficient way to learn.

In all, the present work does not satisfy the needs of the practitioner in an extremely critical area of therapeutics. One must recommend that the physician continue to carefully examine current literature or investigate other collative works which are becoming available.

MICHAEL J. REICHGOTT, M.D.

CELLULAR ASPECTS OF NEURAL GROWTH AND DIFFERENTIATION—UCLA Forum in Medical Sciences—Number 14—Proceedings of a Conference held November, 1969, sponsored by the School of Medicine and the Brain Research Institute, University of California, Los Angeles—Edited by Daniel C. Pease, Chairman and Editor, Department of Anatomy, University of California Press, 2223 Fulton Street, Berkeley, Ca. (94720), 1971. 520 pages, \$25.00.

The nervous system, unlike the other organ systems of the body, undergoes the most complex and diversified morphological, structural and functional metamorphosis as it develops from a population of primitive cells which makes up the embryonic neural crest. Although recent advances in neurobiology have provided fragmentary information concerning neural growth and differentiation and development of the nervous system—as well as the influence of certain homeostatic, nutritional and endocrine factors on these fundamental biological processes—the basic mechanisms which control these processes are virtually unknown.

A conference held in November, 1969, under the auspices of the Brain Research Institute of the University of California, Los Angeles, brought together 38 prominent neurobiologists, representing a variety of disciplines, who reviewed the present state of our knowledge and discussed the future direction of investigations into the cellular aspects of neural growth and differentiation. The presentations and discussions which make up the volume under review reflect the sophisticated techniques which have been developed to study a complex problem which is directly relevant to clinical developmental neurology.

The chapters which deal with the morphological aspects of the basic topic point to the complexity of the mechanisms involved in cellular growth, differentiation and migration, cellular interaction and interconnections. The chapters include discussions concerning the effects of cortisol and epinephrine on the differentiation of glial cells in tissue cultures; the morphology and development of neuroglial cells, comparing light and electron microscopic techniques; developmental aspects of synaptology; the interaction of axonal and dendritic elements in the developing and the mature synapse; one chapter features an elegant discussion of the development of the avian visual system. Of particular interest is a chapter on the investigation of neural development utilizing tissue culture techniques.

Very little imagination is required to visualize how this orderly, precise and predictably reproducible sequence of biological events can be disturbed and altered by extraneous factors—physical and chemical—and how such a disturbance may ultimately result in congenital malformations of the nervous system and mental retardation. Considering the incredible intricacy of the multitude of processes involved in the development of the nervous system, it seems remarkable that the majority of brains are both structurally and functionally normal.

The chapters on the metabolic aspect of neural growth and differentiation discuss such topics as the relationship of thyroid function to the developing nervous system, hormonal and nutritional influences on brain development and the metabolism of proteins, nucleic acids, biogenic amines and lipids in the developing brain. Of particular interest are the reports of investigations on two brain-specific proteins, presumed to be of glial and neuronal origin respectively. Their identity provides a most useful marker heretofore not available and the study of these proteins during development and degeneration may help elucidate the basic nature and pathophysiology of a number of diseases of the nervous system. The isolation of these proteins and nerve growth factor, a pro-

tein with growth-promoting properties which is also discussed in two of the chapters, is a relatively recent development in neurobiology.

This interesting report, which is amply illustrated and which contains many graphs and tables, should prove invaluable to the sophisticated student of developmental neurobiology and to those who wish to become better acquainted with the complexities of the maturing nervous system. Discussions by the "pros" in the field, which follow each chapter, are particularly lively, stimulating and challenging. The remarkable technical advances in the field which are described in each presentation are a reflection of man's ingenuity and his striving toward a better understanding of the forces which have created his physical and intellectual attributes.

PIERRE M. DREYFUS, M.D.

* * *

THE MODERN FAMILY DOCTOR AND CHANGING MEDICAL PRACTICE—John P. Geyman, M.D., Associate Professor and Chairman, Division of Family Practice, University of Utah College of Medicine, Salt Lake City, Utah; Formerly Director, Family Practice Program, Community Hospital of Sonoma County in affiliation with University of California School of Medicine, San Francisco. Appleton-Century-Crofts, Educational Division, Meredith Corporation, 440 Park Avenue South, New York City (10016), 1971. 297 pages, \$8.50.

"Family medicine needs a textbook medical students can carry under their arms." A medical educator made this observation several years ago. This book, probably the first on this subject, is still not a medical textbook in the usual sense of the term since it is not clinically oriented.

Much has been written about present-day deficiencies in health care services. This information and these opinions have been organized into chapters in book form. A similar number of words have been published in articles about family medicine, family physicians, and family practice but no one has heretofore organized them into a book. Furthermore, the author offers the proposal and reasons why development of family practice will solve most of our health care deficiencies.

Portions of the book are devoted to defining terms, and several, such as the difference between general and family practice, differ markedly from those of others working toward developing this field. One omission which should be noted was the very important step taken to elicit the help of medical educators by inviting representatives from the university professors and specialty boards in medicine, pediatrics, psychiatry, obstetrics and surgery to participate in the drafting of the "essentials" for residencies in family practice.

Nevertheless, the book is an exhaustive compendium of data and information about family practice and the education of physicians and other health personnel to provide this type of primary care. It starts by summarizing the history of general practice and then tells how and why the new specialty of family practice came into being. He cites many authorities in the health care field and it is undoubtedly important that their observations are called to our attention. However, of greater interest and probably more valuable are the opinions and views of the author drawing upon his vast experience in training, practice, and now teaching under such chapter headings as: "Requisites for the Family Doctor," "Nature of Family Practice," "Behavioral Science in Family Medicine," "Some Misconceptions about Family Practice," and "Some Personal Satisfaction in Family Practice."

This book should be helpful to medical students and many medical educators to better understand this new specialty.

LELAND B. BLANCHARD, M.D.



Traffic Medicine

A Symposium

EDITOR'S NOTE: *Almost a year ago the Editorial Board noted that deaths and injuries due to automobile crashes in this nation in any one year actually exceed the total number of deaths and injuries sustained by Americans in the Vietnam War since it began.* This can and should be viewed as an epidemic of major proportions adversely affecting the health of the nation, and as such, a matter appropriately of concern to physicians and the medical profession.*

Most physicians are poorly informed about what is and is not known about the causes of automobile crashes, what occurs when they happen, the mechanisms which produce the injuries that result, and the problems of immediate care for the persons who sustain these injuries. In fact the scope and subject matter of what might be called "Traffic Medicine" and the role of physicians and the medical profession in advising patients, the public and automotive and highway engineers, have received very little attention.

The Editorial Board suggested that a special issue of CALIFORNIA MEDICINE might focus upon these problems of "Traffic Medicine" and begin to identify and define the scope and subject matter. The editors agreed. A guest editor for this purpose was selected. Dr. Kenneth E. Duffey is a general surgeon in private practice, who has far more than a casual knowledge of what is involved in "Traffic Medicine." This issue of CALIFORNIA MEDICINE, so far as is known, marks the first time an attempt is made to examine authoritatively the problems of "Traffic Medicine" in a professional journal of general medical interest.

The editors wish to express their thanks to Dr. Duffey for this important contribution to the medical literature, and hope that it will be of both professional and personal value to our readers, most of whom take care of patients and drive automobiles. —MSMW

***War in Vietnam—1961-1970**

Deaths:	
Battle	44,249
Non-battle	9,067
Total	53,316
Wounded	293,442

Motor Vehicle Accidents—1970

Deaths—Total U.S.	54,800
Disability Injuries—Total U.S.	2,000,000
(Beyond day of accident)	

Traffic Medicine

An Editorial Overview

KENNETH E. DUFFEY, M.D., *San Francisco*

CORRECT A CONTAMINATED food and water supply, treat the victims, identify the carriers, and you take the major steps necessary to stamp out a typhoid epidemic. A major health triumph results because of the isolation and control of a few variables readily identifiable.

No comparable health triumph may be expected in stamping out the epidemic of motor vehicle injury and fatality. Unlike that of a typhoid epidemic, control of automobile collision injury is concerned with identifying and coping with a large number of factors and unknown variables. New ones continue to be added and established ones may be subject continuously to change.

It is the purpose of this issue of CALIFORNIA MEDICINE to reassess some of the areas of concern in what may be called Traffic Medicine and to examine what has been done about them. A complete coverage of the subject matter would be encyclopedic. Many important aspects of traffic medicine have not been touched upon here.

The present auto vehicle death and injury epidemic was non-existent during the childhood of many persons still living. Seventy-six years ago the first American-made automobile was sold in the United States. In 1903 the Ford Motor Company was founded and five years later production of the Model T began. By 1915 there were about three million motor vehicles in the United States. In the same year about seven thousand deaths related to motor vehicles occurred.

In the next 53 years the number of vehicles in

the United States increased to over 100 million. By 1968 the number of deaths due to motor vehicle operation was more than 55,000. In California during the '60s the number of motor vehicles rose from 8 million to 12.5 million. Motor vehicle fatalities rose from 3,500 to 5,000 a year.

Today medicine is faced with the fact that motor vehicle fatalities are the principal cause of accidental death for all age groups under 75 years and in second place for persons over 75.

It is significant that young men are particularly vulnerable. The age group most associated with motor vehicle fatalities is the 15 to 24 year group. Over 40 percent of the total mortality of this age group is related to motor vehicle accidents, and 80 percent of those who die are male.

A motor vehicle accident may be divided into a pre-crash, crash, and post-crash phase. During the rising epidemic, physicians have been on the receiving end of the post-crash human wreckage. Neither medical science nor any other discipline alone has developed the capability to control the human, vehicular, and environmental factors in the pre-crash phase. The multidisciplinary nature of the problems in this phase requires knowledge and skill from many professions and specialists in many fields.

Many important contributions to the problems have been made in the pre-crash and crash phases. The automobile industry, although usually requiring external prodding, has incorporated safety features in automobiles. For example, the Cornell Aeronautical Laboratory's Automotive Crash Injury Research projects began in the early 1950's. The common belief before the publication of the Cornell study was that ejection from a car colli-

Dr. Duffey is the Guest Editor of this special Symposium on Traffic Medicine.

Reprint requests to: K. E. Duffey, M.D., 909 Hyde Street, San Francisco, Ca. (94109).

Crash Course

Until 1968 Dr. Kenneth Duffey, guest editor of this special edition on Traffic Medicine, had little professional interest in that subject beyond the knowledge which a general surgeon might be expected to have in the principles of trauma management. Then came a call from the Governor's office that brought about a great change. Would Dr. Duffey, the caller asked, serve on the Governor's Auto Accident Study Commission? And after 24 hours of reflection, Dr. Duffey said yes.

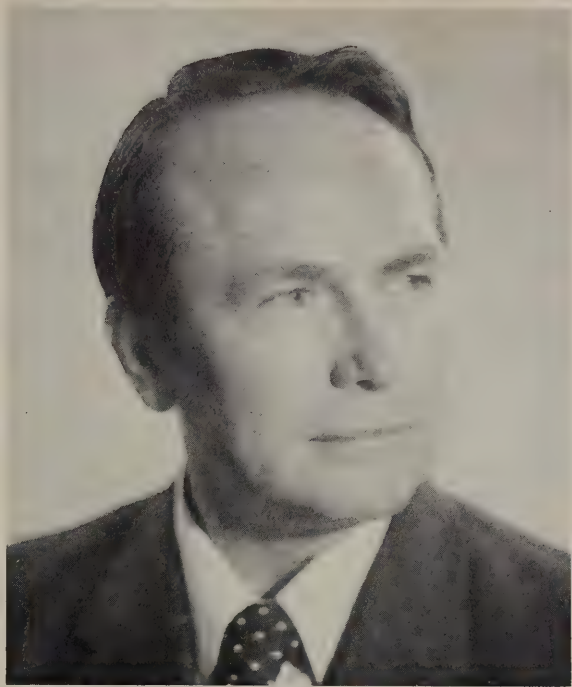
With that answer the appointee was sped into a course of informal but intensive schooling in a wide range of subjects bearing on traffic safety. His instruction came from association with the engineers, physicists, jurists, statisticians, insurance people and others who served with him or were consulted by the Study Commission.

"I had to learn fast about things outside my own field just to keep up with the interim reports that were required of the Commission," Dr. Duffey said. One almost immediate personal effect of what he learned was that he found himself unwilling even to sit in a parked car without his lap-belt and shoulder-harness latched.

After the Governor's Study Commission had completed its work and been disbanded, Dr. Duffey was called as a consultant to the State Senate on the medical aspects of proposed legislation concerning motor vehicle safety. That his interest continues is attested in his willingness to bring together the articles by experts on Traffic Medicine that appear in this issue.

The guest editor is not a tyro in the writing business. Shortly after his return from overseas duty in World War II to Air Force headquarters in Washington, D.C., he and another officer wrote a book on the air war in the South Pacific.

He had entered the Air Force immediately after graduation from the University of California at Berkeley with a bachelor's degree in political science, but during the war years he acquired a deep interest in medicine, and upon discharge and return to his native San Francisco he entered Stanford University School of Medicine.



Dr. Duffey is a diplomate of the American Board of Surgery and a Fellow of the American College of Surgeons. Significant in the business at hand, he is a member of the Board of Directors of the American Association for Automotive Medicine. He is engaged in general surgical practice in San Francisco, where he lives with his wife, Virginia, and their three children.

"Traffic Medicine is a wonderful subject for all doctors to develop an interest in," Dr. Duffey believes. "The problems are really an exercise in practical ecology to a large extent and there is room for all newcomers. Some areas in the country are better organized in this field than California, but this will change because our needs are so great." Dr. Duffey advocates membership in the American Association for Automotive Medicine for physicians generally. "Just write for an application, care of CALIFORNIA MEDICINE, and I will accommodate."

sion was safer than remaining inside the car. The Cornell study proved this to be a fallacy. Donald Huelke has described dramatically in his article in this issue how the use of improved door latches by the automobile industry after the Cornell study has reduced cases of multiple trauma and death. As a result the frequency of fatal injuries which was 12 percent among ejected occupants has been reduced to 2.5 percent among the non-ejected. Huelke has been among the leaders in research on the crash phase of motor vehicle accident injuries. In association with his co-worker, Gikas, Huelke made careful studies that pointed to the importance of seat belts, now standard

equipment by law. His article describes other important modern contributions.

The role of alcohol in vehicular accidents has become so well understood in modern society that no longer are arguments seriously advanced that the power of the state invades the personal freedom of the individual by legislative establishment and police enforcement of presumptive limit and implied consent laws affecting drinking drivers. That alcohol is involved in well over 50 percent of the fatal accidents in the United States (about 30,000 deaths in 1969) is well known.

Julian Waller has been in the forefront among

the investigators of the role of alcohol in traffic medicine. An important concept he emphasizes is that not the occasional social drinker but the problem drinking alcoholic in the general population is responsible for most of the accidents involving alcohol.

As a result of study by the Governor's Auto Accident Study Commission, the California State Legislature in 1971 passed a resolution of intent to differentiate among classifications of alcoholic vehicle drivers. This is a first legislative step toward identification of problem alcoholics among registered drivers. It may be hoped that once they are identified and treated, chronic problem drinkers can be so controlled that the accident rate associated with them will be reduced.

As Waller points out, no research studies are yet available to document the effects of mind-altering drugs, such as amphetamines and marijuana, upon driving.

What is the "third collision"? Why wear a seat-belt? Physicians who are also physicists or those who have saved their pre-medical textbooks may be able to answer the seat-belt question by recall or by looking up the answer concerning the me-

chanical forces involved. Arnold Siegel, a trauma research engineer, has written about these forces in his article on Automobile Collisions, Kinematics and Related Injury Patterns. The article is in keeping with the multidisciplinary needs of the physician in order to have an understanding of the crash phase of motor vehicle injury and prevention.

A stated goal of contributors Stanley Schuman and Donald Pelz to this issue is "to accelerate the naturally occurring process of self-awareness, responsibility, and driving maturity" among young drivers in their teens and early twenties. The dreary statistics concerning the high fatalities of male drivers in this age group have been mentioned above.

The goals of these two contributors are probably among the most difficult to achieve within the pre-crash phase. Independent variables of behavior within this age group are elusive.

The Guest Editor gratefully acknowledges the contributions and cooperation of the contributors to this issue who have been gracious with their time and talents.

KENNETH E. DUFFEY
Guest Editor

SLOW EYES AT FREEWAY SPEED

Recently Wayne L. Erdbrink in San Francisco and I tested special visual function—vision under poor light, vision against standardized glare, and seconds for recovery to normal—in 162 persons. A total of 125 had uncorrected vision of 20/50 or better and were corrected to 20/20. None had any ocular pathology. Sixteen of these patients (roughly 10 percent) blew the whole test. Remember these were patients with apparently normal eyes, no ocular pathology, and in the age group 16 to 74. Either they were unable to say, "Up," "Down," "Left," or "Right" every 1.5 seconds or they couldn't get through. This sort of worries me. But I do believe that about 10 percent of the population is unable to make these modestly quick decisions that are called upon in transportation ophthalmology. This disappoints me, but I think you have to recognize that there are some people coming down the San Diego Freeway who just don't make these decisions. We therefore have to engineer to accommodate them.

—ARTHUR H. KEENEY, M.D., Philadelphia
Extracted from *Audio-Digest Ophthalmology*, Vol. 9, No. 5, in the Audio-Digest Foundation's subscription series of tape-recorded programs. For subscription information: 1930 Wilshire Blvd., Suite 700, Los Angeles, Ca. 90057

Host Factors in Dangerous Driving

Evidence for the Design of Countermeasure Programs

STANLEY H. SCHUMAN, M.D., DR.P.H., AND
DONALD C. PELZ, PH.D., *Ann Arbor*

THE ROLE OF THE DRIVER IN COPING with present day traffic is so complex that planning for future transportation systems leans heavily on eliminating host factors behind the wheel. In the meantime a large proportion of highway crashes implicate driver error as well as defects in the car-roadway-traffic environment.

It should not surprise us that learning a complex set of skills, perceptions, habits, and attitudes for competent driving does not come easily. Unfortunately, the consequences of these learning errors are manifested in a relentless toll of death, disability, and property damage due to motor vehicle accidents.

Evidence from Fatal Crashes

In Michigan, cooperative studies with the State Police and the Highway Safety Research Institute have provided a means of monitoring traffic deaths with modern computer methods. Patterns and trends of the fatalities provide clues for further studies and evaluation of existing programs, and can lead to the development of new programs.¹ For example the data routinely collected by the police on age of driver involved in fatal crashes is important. The age of the driver involved in a fatal crash indicates a "host factor" in the epidemiologic chain of events. Specifically, a four-year analysis of Michigan's fatal

accident drivers reveals that of the 802 "excess"* drivers involved during the two worst years (1968 and 1969) compared with the two better years (1967 and 1970), 390 or 49 percent were aged 24 or younger. Thus nearly half of the statewide increase in dangerous drivers was concentrated in the younger age group which constitutes only 22 percent of the licensed driving population.²

Such data tend to reinforce our natural concern for young drivers who are consistently over-represented in every state or national collection of fatal statistics.

A different analysis is presented in Chart 1 which presents fatal driver involvement by single year of age for the last three years in Michigan. The graph line for females in this case is rather flat except for small rises at ages 18 and 21. The male line indicates a consistent rise for beginning drivers from age 15 to age 18, a sharp decline at age 20, with another sharp rise at ages 21 and 22. The distinct contrast of younger males with older males (over age 30) and with females of all ages is not new; however, the dip in male drivers at age 20 was unknown to observers in Michigan until computerization produced the data analysis by single year of age. The data for each of the years 1968, 1969 and 1970 show the same dip; this graph summarizes a recurring phenomenon for some 9,046 drivers. Speculation about the dip at age 20 led to further analysis by segregating the drivers into the police-reported categories: "had been drinking (23 percent)," "had not been drinking (53 per-

Professor of Epidemiology, School of Public Health, University of Michigan (Schuman); Program Director, Survey Research Center, University of Michigan (Pelz).

Reprint requests to: S. H. Schuman, M.D., Department of Epidemiology, School of Public Health, University of Michigan, 109 Observatory Street, Ann Arbor, Mich. 48104.

*The number by which the worst years exceeded the better years.

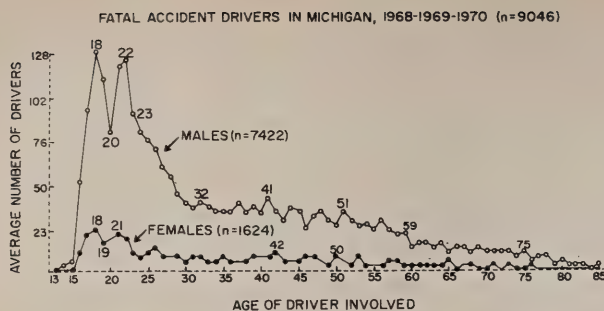


Chart 1.—Variations in the involvement in fatal crashes by age and sex for 9,046 Michigan drivers: evidence of a consistent sharp decline for 20-year-old male drivers in 1968-1969-1970.

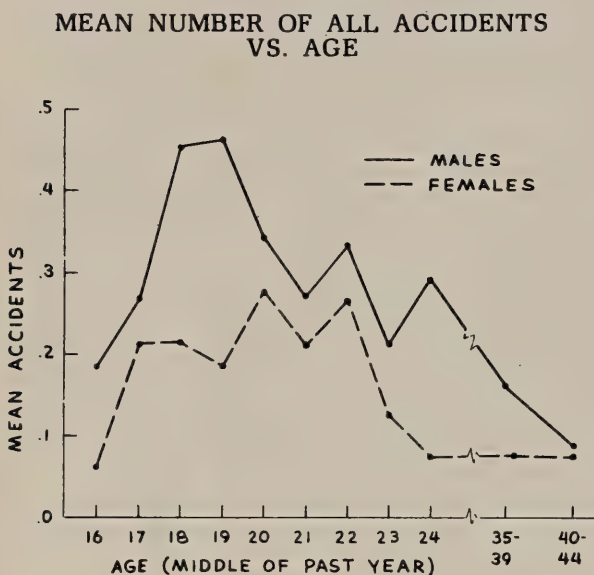


Chart 2.—Variations in mean accident rates per year among 2,773 interviewed suburban Michigan drivers, by age and sex.⁴

cent),” and “drinking not stated (24 percent).” As one might expect, since the legal drinking age in Michigan was 21 until January 1, 1972, the 18-year-old peak represents non-drinkers, the 21-22-year-old peak represents drinking drivers, and the “drinking factor unknown” drivers show a bimodal configuration similar to that in Chart 1. Further study would suggest that the less dangerous period at 20 is the valley between the peak of inexperience-overconfidence and the peak of driving-after-drinking.³ The recent change in legal age of drinking (to age 18 in Michigan) will be watched closely for possible effects on the fatal driver curve.

Evidence from Survey Research

The file on fatalities speaks clearly on certain patterns but then is silent on much-desired in-

MEAN NUMBER OF VIOLATIONS PLUS WARNINGS VS. AGE

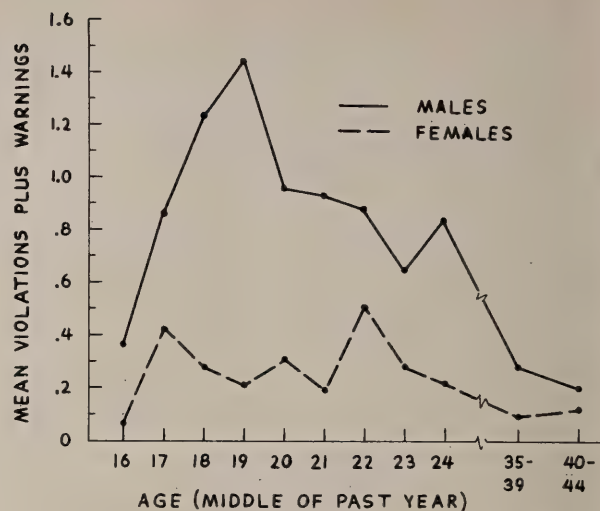


Chart 3.—Variations in mean rates of moving violations-and-warnings among 2,773 interviewed suburban Michigan drivers, by age and sex.⁴

formation on host variables such as number of miles driven, amount of week-end driving, day-night driving, pattern of driving after drinking, driving when angry or upset, age of learning to drive, ownership of the car, attitudes toward driving, and influence of passengers on driving. These host variables require special studies of probability samples of licensed drivers in large enough samples to provide adequate comparisons. In a probability sample of 3,000 suburban Michigan drivers, detailed interviews provided some interesting insights.⁴ In Chart 2, mean accident rates for drivers during the past year are plotted by age and sex with the expected male excess prominent at age 18-19 and a decline at ages 20-21 reminiscent of the fatal driver pattern (Chart 1). In Chart 3 the self-reported moving violations and warnings are plotted by age and sex with an even greater discrepancy between young male and young female drivers, and with a tapering off of illegal driving practices for men at age 20 and for women somewhat later at age 23. The data in Charts 2 and 3 needed to be rigorously analyzed with mileage and kinds of driving held constant, and this was done for the larger sample of males in a separate publication by the authors, using multivariate analysis. Even after such adjustment of the accident and violation rates, the major age and sex differences remain with the same peaks at ages 18 and 19 for men.⁵

Variations in Motivations and Driving Styles

The root causes for dangerous driving practices are complex and probably reflect the well known axiom: "One drives as one lives." Troubled lives lead to troubled driving; for example, national death rates indicate that young divorced or widowed females have driving records as poor as young single men. Selzer and others have described the complex host factors in the problem drinker who mixes suicidal and homicidal tendencies behind the wheel.⁶ Our findings from young driver interviews suggest that a period of turmoil at ages 18 and 19 for men includes changes in life style (school, job, army, living arrangements, drinking, starting or stopping an engagement, taking on new responsibilities, debts and the like) and changes in driving style (more competitive driving, more close calls, more time spent in and around cars, growing confidence, longer trips, more weekend driving, less use of seat belts). A few of these findings are indicated in Table 1 (hostility variables), Table 2 (driving motivations) and Table 3 (life changes) with correlations of such variables with crashes and violations-plus-warnings. Hostility feelings toward things and people (peers and

adult authorities) are highly correlated with dangerous driving for young males in both crashes and violations; for older females the correlations are mainly with violations. (Could some of these 35 to 44-year-old women be under menopausal stress?) Interestingly the older male seems to have other outlets than driving infractions for his hostility feelings. In Table 2 key correlations with crashes are found for males (older and younger) and for younger females for driving after an argument. Distracted or inattentive driving shows up for older males involved in crashes. The long list of correlations of young male characteristics with violations suggests a range of risky and careless driving practices which may go along with feelings of growing confidence behind the wheel which may exceed actual skills. The relative lack of significant correlations in Table 3 suggests that life changes may be difficult to measure and may be quite selective in their influence on driving; certainly negative marital events have a potential for risky driving (violations for three groups and crashes for young females). Older females who change jobs have more crashes. These complex sets of data must be interpreted with caution and reinforced by further study.⁷

TABLE 1.—Hostility Variables as Correlated with Crashes and Violations-Plus-Warnings in Past Year, Adjusted for Exposure, in Four Groups of Drivers^a

	Young males	Older males	Young females	Older females
<i>Correlations with crashes</i>				
Anger—things (3 pt.)	.053*	.056	.077	.100†
Anger—people (3 pt.)	.046†	-.033	.038	.036
Anger—overt/covert (5 pt.)	.061*	.005	.054	.094
Rebellion index (3 pt.)	.069**	.006	.151**	.114*
Peer hostility index (4 pt.)	.067**	.046	.078†	.117*
<i>Correlations with violations-plus-warnings</i>				
Anger—things	.095**	-.016	.077	.163**
Anger—people	.137**	-.040	.093*	.071
Anger—overt/covert	.138**	-.033	.114*	.175**
Rebellion index	.061*	-.026	.075	.212**
Peer hostility index	.099**	-.011	.063	.163**
Maximum number	1672	303	483	315

^a"Young" = 16-24 years; "older" = 35-44 years. Shown in parentheses after each variable is the number of categories; e.g., "anger—things" was scored: 3 = smashed something, 2 = felt like it, 1 = neither; a few not answered were omitted. "Anger—overt/covert" was scored: 5 = hit someone, 4 = smashed something, 3 = felt like hitting, 2 = felt like smashing, 1 = none of these.

Statistical significance is indicated by:

**p < .01

*p < .05

†p < .10 (borderline significance)

TABLE 2.—Driving Motivations as Correlated with Crashes and Violations-Plus-Warnings in Past Year, Adjusted for Exposure

	<i>Young males</i>	<i>Older males</i>	<i>Young females</i>	<i>Older females</i>
<i>Correlations with crashes</i>				
Owens car driven most (3 pt.)	-.026	-.064	-.030	-.146
Assertive driving index (4 pt.)	.034	.013	.088†	-.033
Driving after argument (2 pt.)	.101**	.162**	.131**	.088
Distracted driving (3 pt.)	.052*	.188**	.078†	.022
Escape driving (3 pt.)	.059*	.130*	.102*	.175**
Competitive driving (2 pt.)	.092**	.064	.086†	.052
Time working on cars (3 pt.)	.022	.044	.029	.025
<i>Correlations with violations-plus-warnings</i>				
Owens car driven	.036	.009	.007	.061
Assertive driving index	.071**	.024	.088†	-.007
Driving after argument	.094**	.006	.135**	.019
Distracted driving	.065**	.129*	.058	.143*
Escape driving	.125**	.094	.077	.156**
Competitive driving	.161**	.119*	.070	-.045
Time working on cars	.124**	.015	.055	-.032

Statistical significance:
 **p < .01
 *p < .05
 †p < .10 (borderline)

TABLE 3.—Life Changes as Correlated with Crashes and Violations-Plus-Warnings in Past Year, Adjusted for Exposure

	<i>Young males</i>	<i>Older males</i>	<i>Young females</i>	<i>Older females</i>
<i>Correlations with crashes</i>				
Positive marital events (2 pt.)	.032	-.073	-.038	-.005
Negative marital events (2 pt.)	.039	.060	.160**	.023
Total family events (2 pt.)	.028	-.027	.042	-.009
New responsibilities (4 pt.)	.014	-.003	.029	.089
Stopped school (2 pt.)	-.054*	-.035	.010	.058
Started working (2 pt.)	.015	-.038	.025	-.058
Changed jobs (2 pt.)	.041	-.038	.034	.140*
Stopped working (2 pt.)	.036	-.017	.055	-.070
Total job events (3 pt.)	.044†	-.050	.049	-.022
<i>Correlations with violations-plus-warnings</i>				
Positive marital events	.022	.016	-.055	-.023
Negative marital events	.084**	.214**	.127**	-.040
Total family events	.052*	.060	.043	-.023
New responsibilities	-.057*	-.074	.010	.030
Stopped school	.030	-.001	.069	-.045
Started working	-.021	-.015	.028	-.014
Changed jobs	.057*	-.021	.031	-.030
Stopped working	.014	.053	-.011	.022
Total job events	.037	-.049	.011	-.007

Statistical significance:
 **p < .01
 *p < .05
 †p < .10

The Ultimate Test: Driver Performance

As in therapeutic or preventive medicine, a variety of regimens are proposed to improve driving; few can stand the test of time or rigorous controlled experimental design and evaluation. Most programs are aimed at training young drivers, or rehabilitative courses for drivers of all ages whose licenses are in jeopardy; their efficacy is difficult to measure.

In April of 1968 in one Michigan high school, the authors field-tested an innovative program aimed at high school seniors who had completed the state-sponsored program of driver education, who had been driving one to one-and-a-half years, and who were entering the crucial 18-19 age period of risky driving suggested by our state police and interview studies. Although it was only a pilot study, involving 19 treated and 114 untreated seniors, the design assured random assignment of subjects and impartial follow-up over a two-year period of official state driving records. The countermeasure program had two components: small group discussions held weekly for seven weeks on the "coping" problems of responsible driving utilizing open-ended "trigger films" and realistic driving situations, and personalized driving letters sent to participant seniors at six-month intervals following the discussion workshop.⁸ The emphasis in the workshop was on realistic appraisal of the complex driving task and personal commitment to peer-agreed goals of better driving performance. Fear methods were avoided and authority-set rules were not imposed on the seniors; rather, they were treated as young adults who wanted to improve their own driving.

The results are shown in Chart 4 where the accidents per 100 drivers per six-month period were similar for both treated and control groups in the first six months following the workshop treatment. Then over the next 18 months the untreated seniors did not show the improvement of the countermeasure group. These data do not reach statistical significance, perhaps because of the small sample treated, but the results are extremely promising. Not only were accidents reduced by 50 percent in number, but severity of crashes, violations, and the repeater rate were similarly reduced by a carefully designed program aimed at a high risk target group of drivers. Further field trials in eleven high schools using a variety of countermeasures were con-

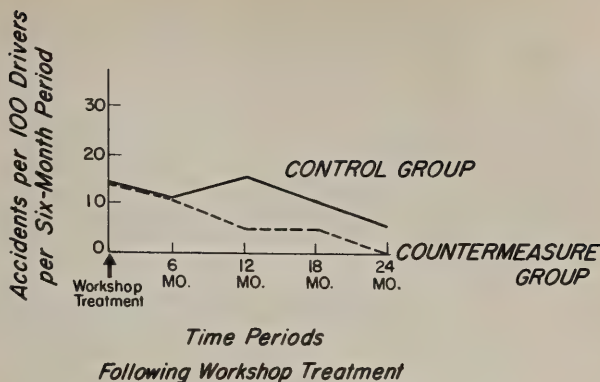


Chart 4.—Evidence of crash reduction in a group of 19 seniors who had "countermeasure" training compared with a matched control group of 114 seniors in one suburban Michigan high school followed over a two-year period, April 1968-April 1970.⁸

ducted in the spring of 1970 and follow-up data are being collected.^{9,10}

Discussion

The complexity and diversity of host factors in dangerous driving may overwhelm those involved in accident prevention to focus on devices and measures which by-pass the role of the human operator. Another approach is to try to identify high risk subgroups of drivers and to reach them with specially designed programs to help them improve their performance. In the case of the young driver, the data indicate that most young drivers do improve as they leave their teens and twenties and enter their thirties and forties; the goal of our efforts has been to accelerate the naturally occurring process of self-awareness, responsibility, and driving maturity.

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Truths, Traps, and Tactics Concerning Alcohol, Other Drugs and Highway Safety

JULIAN A. WALLER, M.D., M.P.H., *Burlington, Vermont*

■ *Ingestion of alcohol by pedestrians is an important factor in severe highway crashes, just as alcohol is important in the injury of drivers and their passengers. Blood alcohol concentrations below 50 mg per 100 ml (0.05 percent by weight) do not increase crash risk, but above that concentration the risk rises rapidly. Three distinct groups—problem drinkers (many of whom do not have blatant alcoholism), teenagers, and heavy social drinkers—make up the overwhelming majority of persons in alcohol related crashes, and countermeasures specific to each group must be applied and evaluated. Past and present countermeasures usually have not been adequately evaluated, or in some cases have been proven ineffective. Countermeasures aimed specifically at reducing losses in addition to those aimed at changing behavior are an integral part of any control program.*

Based on limited evidence, abuse of drugs other than alcohol, with the possible exception of amphetamines, does not appear to be a frequent cause of crashes, and extensive countermeasures probably are not warranted at this time.

MUCH HAS BEEN WRITTEN about the relation of alcohol and other drugs to highway safety. The voluminous alcohol literature was comprehensively reviewed in a 1968 report to Congress.¹ More recently, three reviews have appeared concerning the much sparser scientific data about other drugs and highway safety.²⁻⁴ This paper will include a brief summary of knowledge concerning both subjects. Its main goal, however, is to provide some epidemiologic and administrative perspective which often appears to be miss-

ing as new countermeasures to highway slaughter are being explored.

Data (and "Nondata") Concerning Alcohol

A solid body of data exists about the role of alcohol in highway crashes. This information has been gathered through carefully designed and executed studies over many years and wide geographic areas. Unfortunately, nuances and pitfalls in interpretation abound to confuse even the more sophisticated reader who is not intimately concerned with the field.

The author is Professor, Department of Community Medicine, University of Vermont.

Reprint requests to: J. A. Waller, M.D., Department of Community Medicine, Given Building, University of Vermont, Burlington, Vt. 05401.

Simultaneously, there is a larger body of "non-data"—information, frequently based on official files of state and local agencies, which purports to be accurate, but which is the result of incomplete and nonrandom sampling and use of outmoded methods for detecting and reporting the presence and amount of alcohol. Studies which take these official data at face value are no more accurate than the source documents on which they are based.

What do the data say, and what are the pitfalls? The following facts have been documented:

1. Among drivers who die within six hours after injury about half have alcohol in their blood at the time of death. The proportion with alcohol is even higher among drivers in single vehicle crashes or who are responsible for initiating two-vehicle crashes, and correspondingly is much lower among drivers in crashes initiated by someone else.¹

2. About 80 percent of those with alcohol in such crashes have blood alcohol concentrations of 100 mg per 100 ml (0.10 percent by weight) or higher. Such concentrations are attainable by persons weighing 150 pounds or more only by drinking at least 7½ ounces of 80-proof alcohol (or equivalent alcohol in other proof) in one hour, or correspondingly larger amounts over longer periods.¹

3. In pronounced contrast, among drivers not in fatal crashes but who were interviewed at times and places where such crashes have occurred, only 10 to 15 percent have any alcohol, and only 2 or 3 percent have 100 mg per 100 ml or higher.¹

4. Almost half of fatally injured adult passengers also have alcohol in their systems.¹ When both fatally injured drivers and their passengers have been tested, they have been found in most cases to have similar blood alcohol concentrations.⁵

5. Fatally injured adult pedestrians have alcohol—again usually in high concentration—about half the time,¹ and in most such fatalities involving alcohol the pedestrian rather than the driver is responsible for initiating the crash.⁵

6. Innocent victims make up an estimated 25 to 40 percent of highway fatalities attributable to alcohol. Nevertheless, in the majority of such

severe to fatal crashes it is the alcohol-impaired driver or pedestrian or an equally impaired passenger who is injured.¹

7. Alcohol plays a less frequent but still very important role in crashes resulting in property damage only or in minor injury. It is estimated that at least a million such crashes annually involve alcohol.¹

8. Alcohol is most often found in crashes occurring at night and on weekends.¹ Its presence during holidays, however, including Christmas and New Year's, is no greater than during comparable nonholiday periods.⁶

9. Laboratory studies document that many persons begin to show impairment at blood alcohol concentrations as low as 30 mg per 100 ml (0.03 percent by weight) and that by 100 mg per 100 ml virtually all persons—including those classified as heavy drinkers—show significant impairment when compared with their pre-alcohol performance. (It is important, however, to note that impairment which can be measured precedes intoxication which can be observed.) Nevertheless, epidemiologic data do not show any increase in crash risk at concentrations below 50 mg per 100 ml (0.05 percent by weight) although the risk climbs rapidly after that. At 100 mg the risk of crashing is 6 to 8 times that with no alcohol.¹

Reports or statements of official state and local agencies sometimes contain data decidedly different from those presented above. Usually the reason for the discrepancy is one or more of the following:

1. Blood alcohol concentration studies have been performed on only a limited proportion of fatalities and, as has been amply documented,¹ unless a chemical determination is carried out it is very easy to overlook the presence of alcohol at concentrations below 150 to 200 mg per 100 ml (0.15-0.20 percent by weight). Furthermore, in the absence of a chemical determination, other important biases occur in reporting who does or does not have alcohol.⁷

2. The data analyzed include children and persons who died more than six hours after injury. The absence of alcohol among persons who die after a delay may merely mean that alcohol present at time of injury was metabolized before death.

Even if the data have been properly collected and analyzed, several errors commonly are made

in interpreting them. Thus, it is frequently reported that half of all highway fatalities "are caused by drinking drivers." Three errors are implicit in this statement. First, as was noted earlier, alcohol does not increase crash risk at concentrations below 50 mg per 100 ml, and most non-crash involved persons on the road with alcohol have concentrations below this level. There must be less emphasis on implicating drinking *per se* and more on implicating drinking sufficient to cause impairment.

Second, the role of impaired pedestrians in initiating crashes is ignored. Pedestrians (including children and the elderly, as well as the alcohol-impaired) make up approximately 20 percent of all highway fatalities nationally, and the majority of fatalities in some urban areas. Third, the statement suggests that innocent parties usually are being killed or maimed rather than the drinkers themselves. These distinctions may seem trivial, but they have profound implications for the design of countermeasures.

Who Are the Participants?

In 1953 Bjerver, Goldberg and Linda⁸ in Sweden noted the considerable overrepresentation of problem drinkers among persons with alcohol offenses on the highway. Similar observations were made in the United States during the 1950's and early to middle 1960's by Barmack and Payne,⁹ Selzer and associates,¹⁰ Waller,^{11,12} and more recently by others. Similar studies have been carried out in Canada.¹³ These studies show:

1. Normative (as opposed to normal) social drinkers—that is, persons who usually drink three drinks or less per sitting—and who are the majority of all drinkers, do not usually have crashes or highway violations involving alcohol.¹⁴

2. Persons with serious drinking problems are estimated to make up about two-thirds of those arrested for alcohol-impaired driving or involved in alcohol related crashes. The drinking problems have been identified through personal interviews with the individual or his next of kin,¹⁰ previous contacts with police and other community service agencies,¹² and fatty changes of the liver among fatalities age 25 or older.^{15,16}

3. Teenagers and very heavy (non-normative) social drinkers, the majority of whom are young adult males, appear to make up most of the re-

maining third of individuals in trouble on the highway because of alcohol.^{1,14} Some of the teenagers get into trouble at relatively low alcohol concentrations, perhaps because they are inexperienced drinkers as well as inexperienced drivers. Other teenagers and the young adult males crash at higher alcohol concentrations because frequent, heavy drinking is much more common at this age than it is among the adult population in general.¹⁴ Furthermore, such heavy drinking is considerably more common among the lower socioeconomic classes than among middle and upper socioeconomic groups.

Here again, the data have become distorted in the process of dissemination. First, there has been oversimplification in characterizing the types of persons involved. Before the recent studies the major emphasis—in fact, almost the entire emphasis—in highway safety had been placed upon regulation of social drinkers. Among some highway safety personnel this emphasis now has shifted almost entirely to concern about problem drinkers and "alcoholics." That three identifiable groups (problem drinkers, teenagers, and heavy social drinkers) are involved excessively is a fact that frequently is not recognized.

Furthermore, simplistic dichotomies are being established. According to one recent paper,¹⁷ for example, all persons are either social drinkers or alcoholics. This approach is refuted by excellent work¹⁸ concerned with defining normative drinking practices and the natural history of drinking problems, which may range all the way from heavy social drinking without associated problems through various stages of reversible problem drinking to blatant, readily definable alcoholism (which also may be reversible). Problem drinking certainly includes alcoholism; but just as certainly the definition is not limited to alcoholism.

Another area for misinterpretation has been the nature of contacts with community agencies which persons with alcohol-related crashes or traffic citations might be expected to have either before or after their initial highway events. Such contacts can be expected; but it should not be expected that these contacts will necessarily be overtly alcohol-related. As noted in one of the earliest studies,¹² the alcohol relationship in such contacts often is covert and can be identified at times only by careful probing. Thus, arrests that

nominally were for assault frequently turned out to be the end result of family arguments that started when the husband came home drunk.

Even rarer are convictions for Driving While Intoxicated (DWI). There is now excellent documentation¹⁹ that a substantial proportion of DWI charges are reduced through "plea bargaining" and are reported in the official police records as lesser offenses with no mention of alcohol. Furthermore, there is reason to believe that, despite good evidence of alcohol-impaired driving, many police officers do not even bother to arrest on the DWI charge but initially issue a lesser citation because it entails less work and carries greater likelihood of a conviction. In fact, in the United States the average police officer makes only one or two DWI arrests a year despite the fact that between 2 and 3 percent of drivers on the roads have blood alcohol concentrations sufficiently high to warrant such arrests. Thus, again, contacts with police involving alcohol on the highway are not uncommon, but formal DWI arrests and convictions are rare even among persons well known to the police as problem drinkers.

This discrepancy between informal and formally recorded contacts with community agencies is greater in rural areas where persons with chronically deviant behavior often are well known and are handled through more informal community sanctions than is likely to be the case in urban areas. The observation by some researchers¹⁷ that the drivers who are fatally injured in crashes with alcohol a factor do not very often have previous DWI arrests (although they often have other contacts with community agencies) is more an affirmation of current police practices than evidence that persons with DWI arrests and persons in crashes with alcohol come from different populations. There is in fact evidence that to a substantial degree the two groups come from very similar populations.^{12,14}

Finally, there has been some confusion in replication of the initial studies of liver changes among persons fatally injured in crashes with alcohol a factor. In the initial study¹⁵ it was hypothesized that persons under 25 years old only rarely would have fatty changes of the liver or cirrhosis no matter how much they had been drinking. Persons age 25 or older, however, with high alcohol concentrations should have such changes much more often than would persons in this age group without alcohol or with low alco-

hol concentrations if in fact such fatty changes are attributable to frequent heavy drinking over a period of years rather than being associated simply with acute effects of alcohol. The hypothesis was supported by the data, suggesting that persons fatally injured with high alcohol concentrations are not merely normative social drinkers who only on rare occasions drink too much. Furthermore, in the initial study all degrees of fatty infiltration were counted, because a 25- or 30-year-old person with a drinking problem might be expected to show some fatty changes but not necessarily pronounced metamorphosis, whereas an average social drinker would not be expected to show any fatty changes. Some subsequent studies, however, have not distinguished in the data analysis between persons under age 25 and those age 25 or older. Furthermore, livers with early fatty infiltration have been recorded as normal. When the original criteria have been followed, however, the original study has been validated.¹⁴

What Countermeasures Are Appropriate?

Three basic premises are crucial to the selection of appropriate countermeasures. First is the recognition that the basic goal of highway safety is reduction of losses rather than changing of presumably or documented unsafe behavior, just as the basic goal of communicable disease control is prevention of clinical disease rather than avoidance of infection. (In fact, the function of immunization programs is to create subclinical infection in order to avoid the more serious clinical events.) In choosing countermeasures, therefore, the highest priority should go to those countermeasures which have greatest likelihood of reducing losses, and which do so at minimal social costs. Frequently, this means choosing a countermeasure which is only indirectly related to the basic causal variable identified. Thus, in the case of alcohol caused crashes it may be much easier to reduce losses by moderating energy transfer in crashes through changes in vehicle and highway construction, and by providing better emergency care for the injured, than by attempting to change the behavior of all persons who drink heavily.

Highway safety does not exist in a vacuum, however. The same persons who are contributing excessively to crashes and violations involv-

ing alcohol also are contributing excessively to nonhighway injuries in which alcohol is a factor—to about a third of all arrests in the United States, to homicide, suicide, disrupted families, manpower losses at work, and perhaps, according to new data,²⁰ even to chronic respiratory disease. Because of its spinoff value in these other problem areas as well as in highway safety, therefore, a major effort is warranted to identify problem drinkers—many of whom have early and clearly reversible problems—and to modify their behavior. The strategy, therefore, is first, to improve the ability and willingness of the police to identify alcohol-impaired driving, and to make appropriate arrests. Second, the courts must be convinced to convict in such a way that the involvement of alcohol is identified. Third, adequate presentencing evaluation should be carried out to expose the nature and extent of any drinking problems. Fourth, appropriate treatment facilities must be available and be used effectively by the courts.

Educational programs aimed specifically at teenagers and heavy social drinkers also are needed. The approach up until now has been to tell everyone that even one or two drinks are hazardous. And, as survey data show, many people believe this but very few obey the admonition.¹ Education must be more truthful and more selectively directed to the high risk groups if it is to have effect.

The second basic premise to be recognized is that throughout the nation, but especially in urban areas, impaired pedestrians account for a large part of the alcohol crash problem. Unless and until this is recognized, there will be unrealistically high expectations about highway safety successes achievable through programs aimed at drivers. Control of the pedestrian part of the problem is much more difficult than is protection of vehicle occupants.

The last premise to be understood is that, with very few exceptions, countermeasures to alcohol crashes, no matter how good they sound, either have not been evaluated, or in some cases actually have been proven ineffective. Thus, for example, concerned citizens repeatedly ask, Why don't we try the Scandinavian system of jailing anyone arrested for DWI? We do not try it because the Scandinavian approach has never been evaluated. It may or may not be appropriate in the United States, just as it may or may not be

appropriate in Scandinavia. In fact, the work of Bjerver, Goldberg and Linda,⁸ noted earlier, suggests that the Scandinavian system may not work in Sweden precisely with the same high risk individuals for whom our approaches appear not to be working.

The U.S. Department of Transportation has very appropriately identified the alcohol aspect of highway safety as one of its two highest priority concerns and, equally appropriately, has designated many millions of dollars to an Alcohol Safety Action Program (ASAP). Projects are being set up in several states to institute a wide range of countermeasures, including those recommended above. A moderate amount of the funds for these projects has been set aside for countermeasure evaluation, because it again must be recognized that, no matter how good they sound, these approaches have not been adequately evaluated. The program, therefore, must be viewed as a series of demonstration projects, rather than as a full fledged and already proven action program. In keeping with the demonstration concept, the program must be allowed to grow only at a metered pace so that true evaluation will be possible.

Other Drugs and Highway Crashes

In contrast to what we know of alcohol, our knowledge of the role of other drugs in highway crashes is very modest. For one thing, laboratory methods are not currently available for measuring some drugs, such as marijuana and LSD, in human tissues. Furthermore, as was the case with early studies involving alcohol, effects in laboratory research are often described in terms of absolute dosage ingested rather than in terms of tissue concentrations. The data available so far indicate the following:

1. Based on known pharmacologic actions, many mind-altering drugs are at least theoretically of concern to highway safety. Laboratory studies of the extent to which these drugs impair ability to perform tasks relevant to driving, however, have shown inconsistent results.²⁻⁴ This is in contrast to the almost unanimous conclusion of early studies of alcohol indicating its impairing effects even in small amounts.

2. Anecdotal data are available clearly documenting that some individuals are getting into trouble on the highway because of drug effects, usually from barbiturates or tranquilizers.² Anec-

dotal data, however, are not capable of identifying whether such impairment and resultant trouble are rare or frequent events.

3. Epidemiologic data, as yet available from only a handful of studies, do not identify drug-related crashes as frequent events and, with the possible exception of amphetamine abuse, do not suggest that, from the viewpoint of highway safety, a major countermeasure effort is warranted.²⁻⁴

4. Laboratory studies consistently show that small amounts of alcohol in combination with other mind-altering drugs may create a special hazard to driving because of synergism. The epidemiologic data, however, indicate that most persons fatally injured with alcohol in combination with other measurable drugs in fact have such high alcohol concentrations that for all practical purposes the effect of the other drugs probably is of minor importance. Also of interest is the fact that the drugs found in combination with alcohol commonly are drugs used to treat alcoholism and other emotional disorders.²

The issue of drug abuse raises so many anxieties, however—some quite warranted and others not—that proponents on both sides of the drug regulation question by and large have selected the data that support their positions, rather than look at the entire body of data summarized above. Thus, newspaper articles and representatives of police departments regularly inform the public that impaired driving is one of the major effects of marijuana, although there is no substantial evidence that this is the case. On the other hand, marijuana proponents improperly use the absence of such evidence with respect to highway crashes to suggest that marijuana

has no harmful effects for anyone in any area of functioning. Clearly, neither stand is supported by the existing data. Just as clearly, much more research, and much more sophisticated research, is needed concerning the role of drugs other than alcohol in highway crashes and violations.

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Automobile Collisions, Kinematics and Related Injury Patterns

A. W. SIEGEL, B.A., M.B.A., San Diego

■ *It has been determined clinically that fatalities and injury severity resulting from automobile collisions have decreased during the last five years for low impact speeds. This reduction is a direct result of the application of biomechanics and occupant kinematics, as well as changes in automobile design. The paper defines terminology used in the field of mechanics and develops examples and illustrations of the physical concepts of acceleration, force strength, magnitude duration, rate of onset and others, as they apply to collision phenomena and injury. The mechanism of injury pattern reduction through the use of restraint systems is illustrated.*

FATALITIES ARE EXCEEDINGLY RARE in automobile collisions involving 1967 and later domestically manufactured automobiles at speeds less than 25 mph, even when seat belts are not used. This change has occurred as a result of the domestic automobile industry's collision research and subsequent modifications of its newer automobiles. Accelerating these collision- and injury-reducing changes has been the safety performance standards of the National Highway Transportation Safety Agency, (NHTSA). Many safety or collision prevention devices have been introduced into automobiles since the early 1900's, such as improvements in braking, tire handling and visi-

bility. However, emphasis on motorist injury reduction is a recent development.

Specifically, it began in the United States in 1965, when domestic manufacturers first introduced lap belts as standard equipment. The second major injury reduction factor was introduced in 1966. This was High Penetration Resistant (HPR) windshields. In 1967 the single most lethal device, the steering column, was changed by the introduction of a load-distributing, energy-absorbing steering wheel column. Improvements in the instrument panel, begun in the mid 1960's, were increased year by year. On January 1, 1968, shoulder restraint devices were installed as standard equipment. Broad, wide arm rests, which distributed loads during side impacts, thereby reducing body penetrating injuries, were introduced in 1967 and became increasingly

From the Trauma Research Group, University of California, San Diego.

Reprint requests to: A. W. Siegel, 15137 Valley Vista Blvd., Sherman Oaks, Ca. 91403.

available in 1968. Side impact protection became available for the first time in some 1969 models in the form of a side impact bar integrated with body sheet metal in the side doors. Numerous other changes, such as plastic beading around mirrors, the elimination of narrow radius corners, improvements in the windshield pillars and windshield headers, as well as many other improvements have reduced the severity of injuries.

The early incentive for these changes came from a number of sources, including accident research groups at the Cornell Laboratories, the University of Michigan and the University of California, Los Angeles (UCLA), as well as others. Once the auto industry began to make changes, the changes came rapidly.

In order to reduce occupant injuries, the designers of automobiles had to have information on the mechanics, vehicle dynamics, and occupant kinematics during an automobile collision.

Mechanics is defined as a science which describes and predicts conditions of bodies at rest or in motion under the action of forces, and is divided into three parts: *mechanics of rigid bodies*, *mechanics of deformable bodies* and *mechanics of fluids*. The study of rigid and deformable bodies is further sub-divided into *statics* (bodies at rest) and *dynamics* (bodies in motion). Mechanics is a physical science relating to the time of Aristotle (384-322 B.C.) and Archimedes (287-212 B.C.). However, it was not until Newton (1642-1727) that the fundamental principles of mechanics were satisfactorily formulated. Although Einstein's Theory of Relativity (1905) re-oriented these fundamental principles, Newtonian Mechanics forms the basis of today's Engineering Sciences.

Dynamics is divided into two parts:

1. *Kinematics*—the study of the geometry of a body motion which relates displacement, velocity, acceleration and time without reference to the forces acting upon that body.

2. *Kinetics*—the study of the relation of forces, the mass and the motion of the body. *Biomechanics* is that branch of mechanics dealing with biological systems. All biological systems also follow the laws of nature, as do mechanical, electrical systems; in other words, biomechanics is the application of *statics* and *dynamics* to *biological* systems.

Automobile occupant kinematics is the study

of the collision-induced motion of a motorist during a motor vehicle impact. The kinematics of the occupant are the result of the collision dynamics and the vehicle kinematics. Human injury patterns are a direct result of occupant kinematics and since the kinematics are capable of prediction, to a degree, human injury patterns are capable of prediction. Further, knowledge of the occupant's injury patterns and the collision dynamics is often sufficient information to enable one to predict occupant kinematics and the pre-collision occupant location within a vehicle. As indicated, kinetics is the study of the relationship between applied forces and their effect on the motion of the occupants. The effectiveness of the applied force changing the velocity of an occupant depends upon the magnitude of the forces, that is the size of the force, and the time during which this force is acting. The product of force and time is called the impulse.

The force producing a change in the motion of the body or an occupant is proportional to that change in its velocity and to the sluggishness with which the body yields to change. This latter concept is called inertia. The measure of inertia of a body is called its mass. Momentum is the product of the mass of a body and its velocity. Therefore, this change produced in the motion of the body is measured by the change in momentum.

In 1686 Sir Isaac Newton formulated what are now called Newton's Three Laws. They are as follows:

Newton's First Law—A body continues in its state of rest or of moving uniformly in a straight line, except as it is made to change that state by an external force.

Newton's Second Law—The rate of change of momentum is proportional to the externally applied force and takes place in the direction in which the force is acting.

Newton's Third Law—To every action there is an equal and opposite reaction.

Before discussing acceleration terminology and how it relates to occupant trajectories and injury patterns, it is useful to consider the concept of energy. The energy of a body is its capacity for doing work. The kinetic energy of a body may be defined as the amount of work that body is capable of doing against a force, due to its speed, which tends to bring it to a state of rest.

Of all the terms in use in the collision injury and research field, perhaps the most frequently used term is "g." It is common to discuss a "16g" collision, a "10g" seat, or an "80g" instrument panel. Unfortunately, the term "g" is used to describe these three different concepts of acceleration, force and strength.

Acceleration^{*1,2}

Newton's Second Law of Motion may be expressed by the equation

$$F = ma$$

Where: F is the force acting on the body under consideration
 m is the mass of the body, and
 a is the acceleration that the body is experiencing

Furthermore, the relationship between the weight and mass of a body may be described as

$$w = mg$$

Where: w is the weight of the body under consideration
 m is the mass, and
 g is the acceleration due to gravity (32.2 ft/sec²)

We may divide these two equations and obtain

$$\frac{F}{w} = \frac{a}{g}$$

$G = \frac{F}{w}$ means that the number of

G 's is equal to the force acting on a body to the weight of a body.

Similarly, $G = \frac{a}{g}$ means that the number of

G 's is equal to the ratio of the acceleration that the body is experiencing to the acceleration due to gravity.

The following illustration can be considered and will give meaning to the concepts illustrated above. A car traveling at a velocity of 30 ft/sec., or approximately 20 mph, strikes a rigid abutment and slows down to 0 ft/sec. in 0.6 seconds, or 60 milliseconds. The deceleration the car ex-

*The following discussion is taken in part from a Collision Investigation Training Seminar, September 1969, co-sponsored by the American Medical Association and UCLA. The section on Acceleration Terminology was prepared by Dale E. Runge.

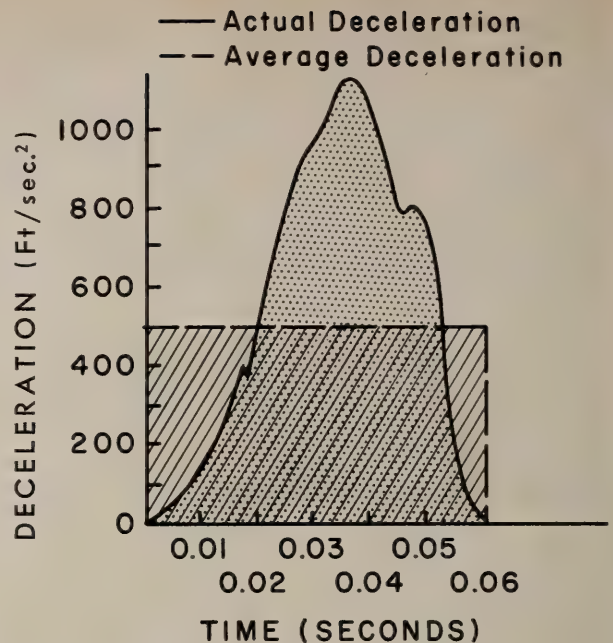


Chart 1.—Automobile Deceleration Pulse for a 20 mph Barrier Crash.

perienced may appear as shown by the solid line in Chart 1.

One can make a simplification by assuming that the acceleration for the entire collision event is a constant value as shown in Figure 1 by the dashed line. This is illustrated by the equation shown below.

$$a(\text{ave}) = \frac{\Delta v}{t}$$

Where: a is the average acceleration in ft/sec²
 Δv is the change in velocity in ft/sec
 t is time in seconds

By substituting into the equation, we obtain

$$a(\text{ave}) = \frac{30 - 0}{0.06} = 500 \text{ ft/sec}^2$$

Again by substituting, we obtain,

$$G = \frac{a}{g} = \frac{500}{32.2} = 15.5 \text{ (average)}$$

In other words, as the car slowed down while striking the wall, it underwent an average acceleration of approximately 16g's.

The following equation can also be derived from Newton's Laws to determine the average deceleration experienced by a moving body as it comes to rest in a certain distance.

$$G = \frac{v^2}{30d}$$

Where: G is the deceleration of a body
 v^2 is the velocity of the body squared (miles per hour)
 d is the distance over which the body is stopped (feet)

Substituting the data from our previous example and re-arranging the equation, the following is obtained

$$d = \frac{v^2}{30G} = \frac{(20)^2}{30 \times 16} = 0.83 \text{ feet} \quad (10 \text{ inches})$$

Thus the vehicle that crashed into the rigid abutment was stopped with 10 inches of deformation. If we wish to reduce the magnitude of the deceleration, we can increase the stopping or crush distance. For example, if we increase the crush distance to 15 inches (1.25 ft.) for our example

$$G = \frac{v^2}{30 \times 1.25} = 11.2 \text{ (average)}$$

Because a vehicle is from 12 to 17 feet long, deceleration will vary in different locations of the vehicle. However, we will not complicate our considerations by these variations.

Force

In the above problem we calculated the average deceleration for the vehicle undergoing the crash in terms of G 's. We can express force in terms of G 's in a similar fashion. If the car in the above discussion weighed 2,000 pounds, what is the average force exerted on it by the wall, in G 's? To solve this problem, we simply rewrite one of the previous equations as

$$F = WG$$

By substituting, we find that

$$F = 2,000 \times 16 = 32,000 \text{ lb (average)}$$

As an additional example of the use of G 's to describe forces, we may consider Motor Vehicle Safety Standard No. 201, which was effective January 1, 1970. This standard concerns itself with occupant impact protection in the interior of passenger cars. It states that under the proper conditions, the deceleration experienced by a 15 pound headform striking the instrument panel at a relative velocity of 15 mph (22 ft/sec) shall not exceed 80 G 's continuously for more than 0.003 seconds (3 milliseconds).

If we ask the question, what is the force ex-

erted on the headform under these conditions, we can answer it by using the equation

$$F = WG \text{ and we find that}$$

$$F = 15 \times 80 = 1200 \text{ lb.}$$

In other words, the headform experiences a maximum force of not more than 1200 pounds. The Standard also indicates that the *duration* of acceleration is important. An individual can tolerate high deceleration forces for very short time durations.

Strength

The third distinct concept expressed by G 's is that of strength. It is common to hear the strength of seats in military aircraft, civilian automobiles, for example, rated in terms of G 's. A "10 G " seat is a seat designed to have a certain strength. In other words, it is designed to withstand a certain force without failing. For this expression of strength to have meaning, we must know what the weight of the occupant will be. If we assume the standard weight of the occupant in military aircraft, for example, to be 200 pounds, then we know the strength of the seat in pounds. This is found by applying the above equation to the present situation.

$$F \text{ (strength)} = 200 \times 10 = 2,000 \text{ lb.}$$

Knowing the strength of the seat in pounds, we can ask the question, What if the occupant only weighs 100 pounds? Again using the above equation,

$$G = \frac{F}{W} = \frac{2,000}{100} = 20$$

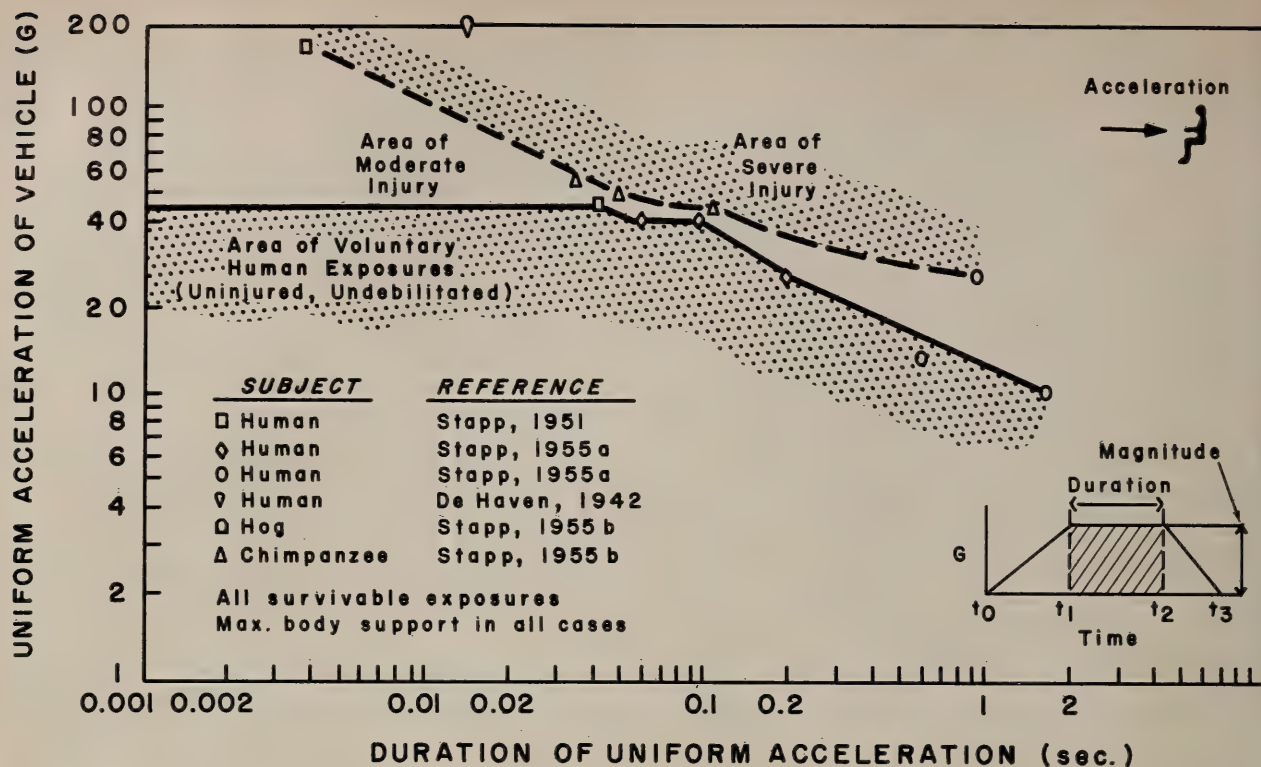
Or, for the 100-pound occupant, the strength of the seat is rated at 20 G 's. In other words, the seat occupied by a 200-pound occupant would fail when the deceleration experienced by the occupant was more than 10 G 's, but the seat occupied by only a 100-pound person would withstand decelerations of up to 20 G 's.

There are a number of parameters which affect the human tolerance to abrupt acceleration (deceleration). In particular, five factors of importance are listed below.

Magnitude—usually expressed in G 's as discussed above.

Duration—the length of time during which the acceleration takes place.

Rate of onset—acceleration is never constant during a collision. The rate at which it changes is the rate of onset expressed in G per second.



Eiband, A.M., A Summary of the Literature. NASA Memo 5-19-59 E

Chart 2.—Human Tolerance to Rapidly Applied Decelerations.

Direction of application—clearly the direction of application of a force relative to the body will determine its danger to the body. In a supine position the application of the force, other things being equal, is less dangerous than if the force is applied directly to, and concentrated on, the temporal region of the head.

Restraint—whether or not the occupant is restrained will change the effect of the abrupt acceleration. During a collision, the deceleration experienced by the occupant is *always* greater than that experienced by the vehicle. In addition, the means by which he is restrained is critical. The restraint system may in part allow the occupant to “ride down” the impact with the decelerating vehicle and not experience the much higher occupant deceleration of a second collision.

The effect of acceleration on human tolerance can be summarized using A. M. Eiband’s compilation of tolerance data, based mainly on military research published in 1959.³ His summary for frontal deceleration is reproduced in Chart 2.

Occupant Kinematics and Restraint

Occupant kinematics during collision and the resultant general patterns of injury have been determined by experimental and clinical collision research, and are predictable. Early full-scale collision experimentation with anthropometric dummies during the 1950’s developed the fundamental patterns of impact displacement. Subsequent live collision investigation studies in the 1960’s and 1970’s have refined these kinematics and developed injury profiles for given types of collision and impact speeds.

The following discussion is not complete, but does outline the basic differences between injuries to restrained and unrestrained occupants for a simple frontal collision configuration. The complexity, of course, of any analysis increases with variations in the angle of impact, impact type and the speed of collision.

On frontal impact at low speeds the *unrestrained* driver moves forward in a seated posture and strikes his knees against the lower instrument panel. He continues to move forward

and strikes the wheel column system with his chest. Depending on his height, his head continues forward and strikes either the windshield, the top of the instrument panel or the wheel rim. As impact speed increases, the severity of each contact increases. The passenger occupant continues forward and may strike the face of the instrument panel with his knees and torso. His head moves forward into the roof header, windshield or panel area.

By way of contrast, a lap-belted occupant in a frontal impact moves forward and takes up the slack in the lap belt and then elongates it. Frequently, the knees strike the lower portion of the instrument panel, but at a much lower force level. The occupant then begins to rotate forward after the maximum lap belt load is reached. The driver then strikes the wheel column system with his chest or face. If his chest strikes the wheel column and the impact speed is sufficiently high, his head may continue to move forward into the windshield or into the top of the instrument panel. Other front seat occupants may strike the windshield or instrument panel with the tops of their heads or faces. Rear seat occupants strike the seat top or back as they rotate forward. The energy of these impacts is much lower when restraint is used.

Injuries vary in degree, depending upon the speed of impact, age of vehicle, object struck and occupant physiology, as well as many other parameters. Whether a restraint was used is, of course, the most important factor. Historically, lap-type safety belts have been described as having three primary advantages during collisions:⁴

1. Preventing full body ejection.
2. Reducing the chances of secondary impact with another object by keeping the occupant in the driver's position.
3. Attenuating the forces of the "second" and "third" collisions.*⁵

With the addition of a shoulder belt, complete and total occupant containment within the vehicle is obtained.

Chart 3 is taken from a paper published in 1958 by Severy, Mathewson and Siegel.⁶ It indicates the value of a lap-type safety belt. The

*The "second" collision is that of the occupant within the vehicle. The "third" collision occurs when the essential body organs—heart, lungs, etc. are decelerated within the body.

dashed line shows the pattern of deceleration for the motorist compartment, a 22g peak, with approximately a 10g average. The solid line portrays the lap belt loop load (total), approximately a 5,000 lb peak. The posture of the dummy occupant is described accurately by the silhouette figures. The distances forward of the initial rest point are described by the upper horizontal ordinate and by the angle of the torso change from the original position. The dynamics derived from accelerometer data and high speed motion picture film of this collision showed the forces of impact greatly reduced by the time the occupant begins to rotate forward and prior to striking the interior surfaces within the vehicle. The expected injury patterns are reduced by this force attenuation.

It should be emphasized that a shoulder restraint system prevents rotation, reduces the frequency of contact against the forward surfaces and subsequently reduces body injuries. An example will illustrate this concept, referred to earlier as "ride down."

In a barrier-type crash, a vehicle traveling at about 30 mph, 44ft/sec., will stop with approximately 25 inches of deformation, or 25 inches of crush to the front end. An *unrestrained* occupant, as indicated earlier, will continue forward at the approximate 30 mph impact speed until stopped by the interior of the vehicle. If we assume that the occupant's 30 mph speed must be stopped with approximately 3 inches of crush by the vehicle's interior, plus the occupant deformation, we find that the occupant is undergoing a change in speed from 30 mph to zero in approximately 10 percent of the distance that the vehicle is undergoing during the impact. The occupant is, therefore, losing, or does not have the benefit of, the large amount of vehicle crush available. If the occupant can be restrained or tied to the vehicle itself in some manner so that he can closely associate his deceleration with that of the vehicle, he can gain considerably by lowering his average deceleration. This is the concept of "ride down." He has a much larger and more effective stopping distance and, therefore, has a much lower stopping force. His injury pattern and injury severity will be concomitantly much less.

The simplest but a very effective system to obtain "ride down" is for an individual to restrain

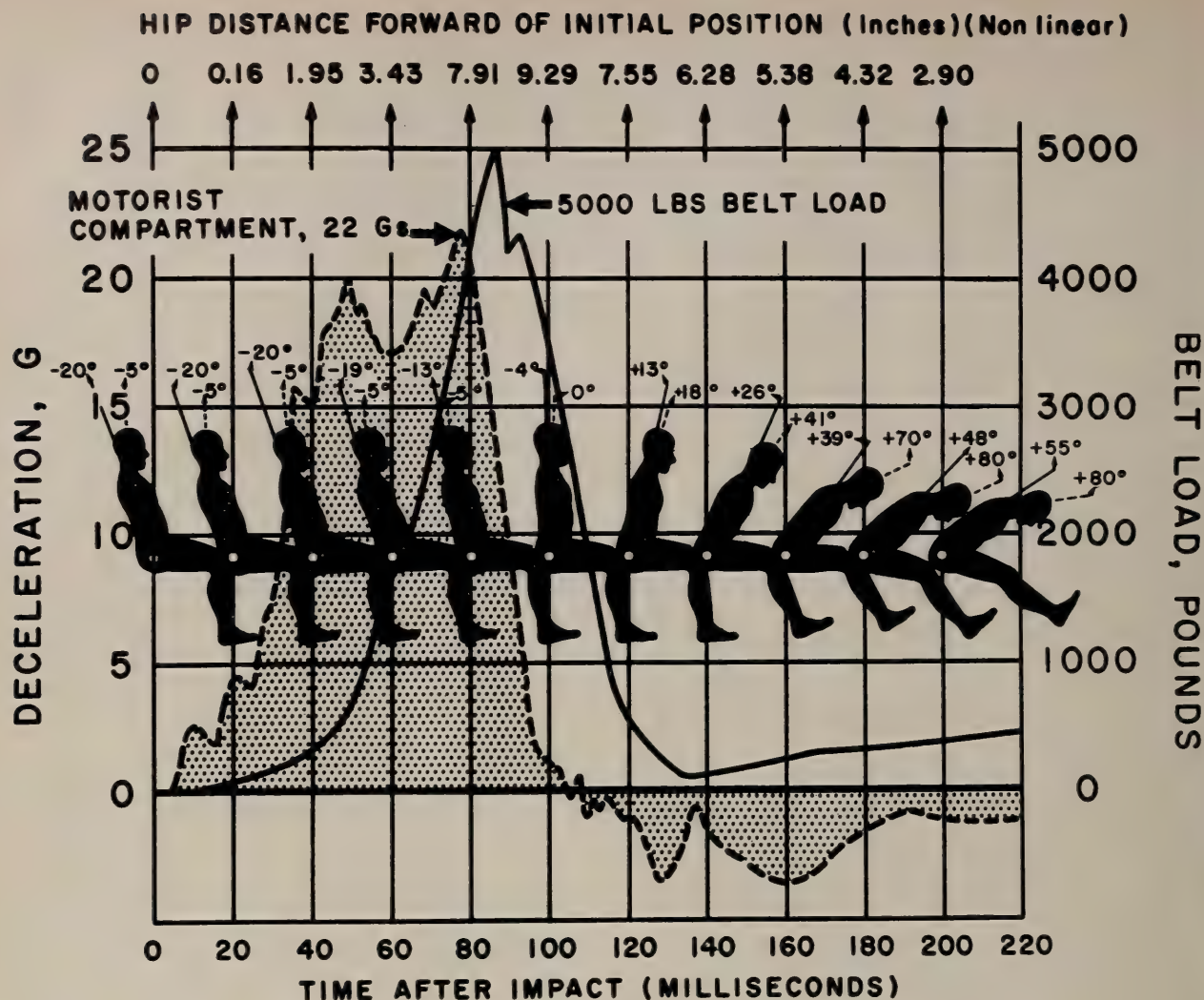


Chart 3.—Kinematics of the Restrained Occupant as Related to Belt Loadings, Head-on Collisions (Nash, 21 mph).

himself by an upper-and-lower torso restraint system.

In summary, then, by using a restraint system, an automobile occupant reduces his collision deceleration and collision forces and subsequently reduces his injury severity by lowering the magnitude of the forces, increasing the duration, lowering the rate of onset of acceleration. Further, the occupant clearly changes the direction of application of collision forces.

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Mechanisms of Injury in Automobile Crashes

DONALD F. HUELKE, PH.D., Ann Arbor

■ *The only way to determine the causes of injury in automobile collisions is through examination of data collected in detailed investigation of crashes. Such data were gathered from a ten-year study of collisions that caused injury to the occupants of the cars. In a comparison of injuries in the newer model automobiles—vehicles equipped with the safety features—with those in older model cars not equipped with the present-day occupant protection devices, significant reduction in injury severity was noted.*

PROBABLY EVERY PHYSICIAN at some time during his professional training or in private practice has been called upon to treat victims of automobile crashes. Most often in such cases he has very little information concerning the mechanisms that caused the injuries. Not infrequently, because of the scanty information given physicians concerning the crash, misimpressions as to how they came about are commonplace. Furthermore, many physicians never have the opportunity nor avail themselves of the opportunity to attend autopsies of crash victims, especially those who are killed at the scene of the crash and taken directly to the morgue.

Ejection

Being thrown from the car has been the leading cause of severe injury and death.^{1,2} These ejection injuries, in general, do not show a specific injury pattern, for occupants thrown out of the car can have injuries to almost any body area, and multiple injury is the rule. Serious head injuries are found fairly often in cases of ejection. This occurs when the occupant strikes the ground or when his own vehicle, or another, rolls over him (Figure 1). Sometimes individuals are violently ejected from the car and thrown

into bridge abutments, trees, utility poles and the like. The human body cannot withstand these tremendous forces; craniofacial trauma and internal injuries to the chest and abdominal contents are commonplace.

In the past, most persons thrown from cars were ejected through doors that had opened during the crash. In the older vehicles, the twisting of the body frame, occupant impact against a door, bending of the vehicle in a horizontal plane, local impact deformation of the vehicle structures in the area of the door latch all contributed to the opening of the door.³ In the newer model cars the latch-striker mechanism that holds the door closed has been improved. Now more often we are seeing injured persons who were ejected through windows.⁴ Especially in rollover collisions the glass is broken and the occupant is partially or completely ejected (Figure 2). The injury patterns of injuries are not necessarily different from those seen previously when ejection was through doors.

Even in the newer models, accidental door opening is still a problem in rollover collisions. It happens sometimes when the outer door button is depressed by the ground or road debris as the vehicle rolls over. This can be prevented, of course, by locking the door from the inside to prevent activation of the latch mechanism from outside.

The author is professor of Anatomy, Department of Anatomy, The University of Michigan, Ann Arbor, and Past-President, American Association for Automotive Medicine.

Reprint requests to: D. F. Huelke, Ph.D., Department of Anatomy, The University of Michigan, Ann Arbor, Mi. 48104



Figure 1.—Driver ejected through opened door. Note available passenger compartment space for survival. Seat belts not worn.



Figure 2.—Unrestrained driver partially ejected through right door window in roll-over collision.

Steering Assembly Impacts

The steering assembly has been a leading cause of death for drivers in automobile crashes.^{5,6} In general, these fatal injuries were due to blunt impact of the chest and abdomen on the steering wheel-column system. Flail chest was not uncommon and blowout ruptures of the cardiac ventricles and lacerations of the aorta at the junction of the aortic arch and thoracic aorta were often noted (Figures 3 and 4). All thoracic injuries of these types were due to deceleration forces rather than to fractured ribs penetrating the heart or aorta. Lacerations of lungs

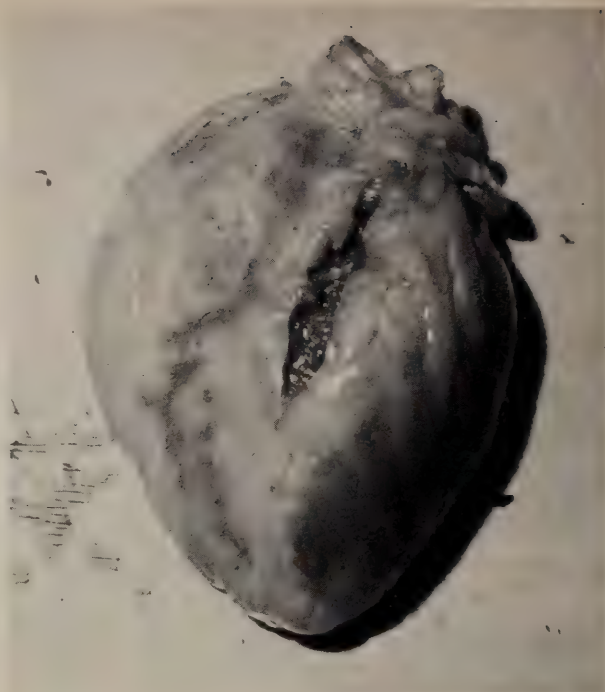


Figure 3.—Blowout fracture of the right ventricle due to thoracic impact on the steering column.



Figure 4.—Aortic laceration following blunt impact against steering column.

were not uncommon, for rib fractures were found to have penetrated lung tissue in forward force impacts of the drivers against the steering col-

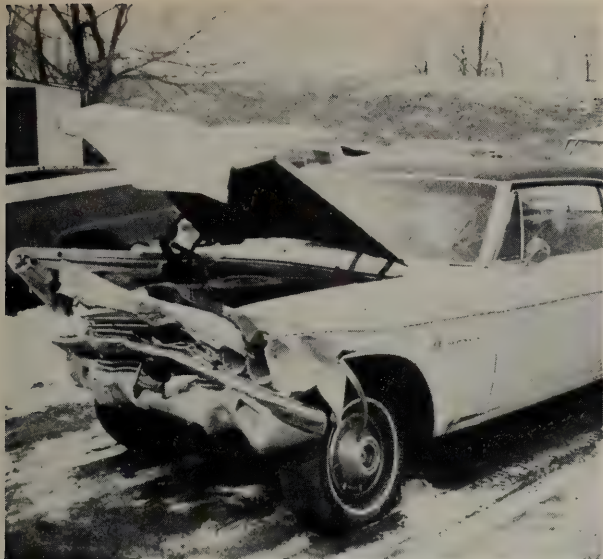


Figure 5.—1966 Chevrolet after head-on, car-to-car collision.

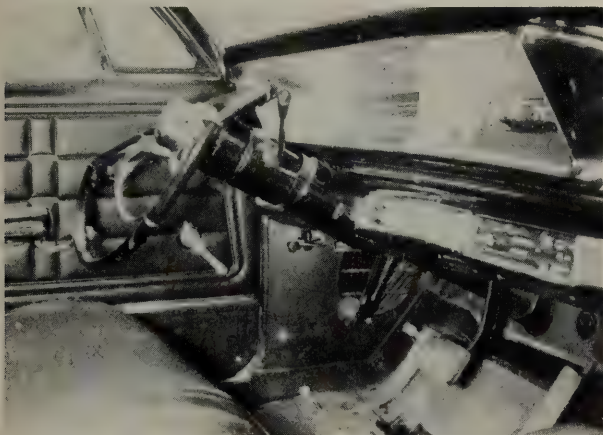


Figure 6.—Deformed steering wheel from driver impact. Driver had multiple rib fractures and right hemopneumothorax.

umn (Figures 5 and 6). Liver lacerations were characteristic of impact to the steering wheel-column system. However, in the majority of these cases this was due to a blow to the thorax rather than to the abdominal area. As the liver is completely housed in the lower right quadrant of the thoracic cavity, blows to the anterior rib cage can compress the liver substance, causing tearing of liver tissue and intraabdominal hemorrhage. Death in such cases was frequently due to exsanguination.

Also noted, but with less frequency, were injuries to the bowel, the mesentery and associated blood vessels. However, these abdominal injuries were less frequent than thoracic trauma when the driver struck the rigid steering column system.

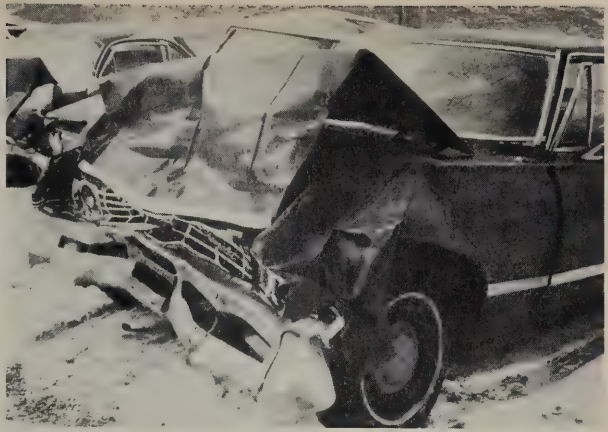


Figure 7.—1967 Chevrolet after head-on collision with vehicle shown in Figure 5.



Figure 8.—Energy-absorbing steering column of vehicle shown in Figure 7. Chest pain was the driver's only complaint of injury from this impact.

Since the recent introduction of the energy-absorbing steering column system in the American-made vehicles, a significant reduction of injury to the thoracic and abdominal contents has been noted in head-on collisions at comparable or even higher impact speeds than those that caused injury before.^{7,8} Drivers are now surviving head-on crashes at higher impact speeds due to the energy-absorbing column. (See Figures 7 and 8.)

Minor or moderate facial lacerations still occur sometimes when the driver strikes the steering wheel rim. Fractured or avulsed teeth, lacerated lips, fractured nasal bones or soft tissue injuries of the forehead are not uncommon. In general, these injuries are found between the hairline and the chin and are on or near the mid-line of the face. They are not limited to high-speed collisions, for even in the lower speed crashes of urban traffic the driver can flex over his seat belt or move directly into the wheel rim with his face (Figures 9 and 10). Though these



Figure 9.—1971 Maverick involved in collision with tree.

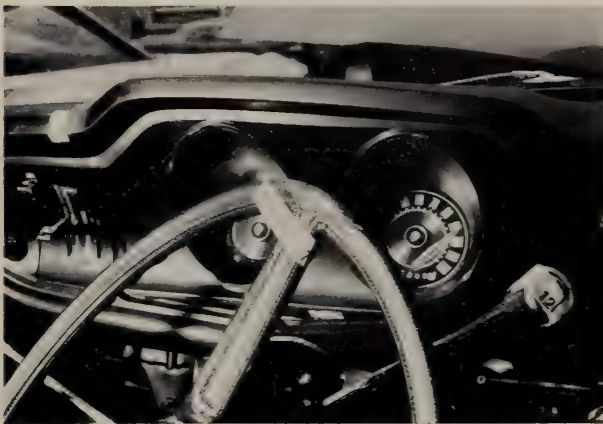


Figure 10.—Driver of Maverick (Figure 9) struck her chin on the steering wheel rim. Deep gouge in steering wheel rim indicates area of extensive chin and lip laceration.

injuries are classified as minor, they may cause some disfigurement and considerable pain, and often dental reconstruction is necessary.

Windshield Injuries

One of the car items that caused significant numbers of injuries to occupants, especially the front passenger, was the windshield. At relatively low head-to-glass impact speeds, the occupant would move forward, striking the windshield glass, usually with his forehead.⁹ As the head jackknifed downward over the instrument panel, it moved forward and on impact fractured the plastic lamina between the two sheets of glass, punching a hole through the windshield. Once it was believed that this breaking of the windshield by the head was what caused the disfiguring lacerations, but now it is known that the deep disfiguring facial lacerations occur when the occupant's head continues downward onto



Figure 11.—Hole in the old type of laminated windshield caused by head impact of an unrestrained passenger.



Figure 12.—Deep forehead laceration from striking the lower margin of the windshield hole shown in Figure 11.

the rigid margins of the lower sides and bottom of the hole. (Figures 11 and 12).¹⁰ In general, these lacerations are not life-threatening but are



Figure 13.—1967 Camaro after severe, head-on collision.



Figure 14.—Arrow indicates the bulging of the new windshield caused by occupant's head impact in crash shown in Figure 13.

cause for concern because of the facial disfigurement.

Beginning in 1966, a new type of high penetration resistant (HPR) laminated windshield was installed on American vehicles. The glass was the same as before but the plastic interlayer was made twice as thick. Also, there are looser bonding characteristics between the glass and the plastic, allowing the plastic to stretch more. Now when a person strikes the windshield, the glass fractures and the plastic bulges forward without tearing. Significant bulges in the windshield are now noted from head contact in the newer model cars even when the contact causes only minor abrasions about the forehead (Figures 13, 14 and 15).¹¹ This one safety feature has greatly reduced the number of facial injuries, and intracranial trauma from impact against the improved windshield is virtually nil. Taken together, the new windshield and the



Figure 15.—Minor abrasions on forehead of front right passenger from contact with improved windshield in head-on collision (see Figures 13 and 14).

energy absorbing column have shown the most obvious injury reduction of the new car safety features.⁵

Instrument Panel Impacts

As often occurs in a head-on crash, the unrestrained occupant in the older model cars moves forward in a seated position, his knees striking the rigid metal lower panel and, not infrequently, his chest and abdomen slamming against the upper portion of the panel. As these heavy metal panels were "non-forgiving," injury could be quite severe. Fractures in and about the knee were fairly common and sometimes there were fractures of the femoral shaft and of the acetabulum. Dislocations of the hip occasionally were caused by transmittal of the force from the knee through the femur directly to the hip area.¹²

In addition, in these forward crashes the floorboards would frequently bend inward, twisting the foot on the ankle and causing fracture-dislocations. Or sometimes the foot would be trapped and the shaft of the tibia or fibula fractured as the occupant's body was thrown forward. Serious and fatal injuries seen in head-on collisions when passengers struck the instrument panel were similar to those of drivers who struck the steering wheel. Multiple rib fractures, flail



Figure 16.—Head impact on upper metal instrument panel. Severe facial and intracranial injuries were sustained.



Figure 17.—Padded upper instrument panel of 1971 Maverick (see Figure 9) struck by the face of a 21-year-old woman passenger. Yielding of the padding prevented serious injury. Contusion of the right eye area was the only facial injury.

chest injury and lacerations of the lung, heart, aorta or liver were not unusual in such cases.

Decreased severity of injury has recently been noted when the instrument panels were padded and better designed as to contour. The padded upper instrument panel offers a head impact area which distributes the impact force through the padding to an underpanel which is made of deformable metal to further absorb the force (Figures 16 and 17).

Facial injuries still are seen but they are less severe with the new panels than the old. Brain injury from upper panel impact is infrequently seen nowadays, and then only in high-speed collisions.

Recontouring and padding of the midportion of the instrument panel have decreased the severity of torso injuries in some collisions. How-

ever, in some cars there is virtually no lower instrument panel, and since the occupant's knees can slide beneath the panel, his chest or the abdomen may take the full force of impact. Severe leg injuries have also been recorded in these circumstances, the bones being twisted by the forward motion of the passenger. Previously the unrestrained occupant struck his knees on the lower instrument panel and flexed forward into the windshield or into the upper panel. Blunt injuries to the torso from striking the midportion of the panel can only be decreased in numbers and severity by restraint systems or by redesigning the panel when adequate data become available on human chest and abdominal impact tolerance.

Rear Collisions

In rear-end collision, the injury of principal concern is that to the neck, and range of severity is from minor sprains to ligamentous tears and fracture-dislocations of cervical vertebrae. It has recently been shown that the head supports, which are standard equipment in the newer cars, are reducing cervical injuries.¹³ It should be borne in mind that head supports function best when they are properly positioned for the occupant. A movable head support when in its lowest position will offer protection for only small persons, and some of them even when extended to the full "up" position may not give complete neck protection for extremely tall riders. Besides the limit they put on the arc of the neck on sudden impact, head-rests may help through the leverage it applies to the entire back of the seat, bending it and thereby further mitigating injury. A factor still to be considered is the greater susceptibility of women to cervical injury from rear collision. This may be owing to their weaker neck structure.

Injury reduction—not injury elimination—has been noted in the newer model cars where safety features have been installed. The ideal situation is to keep the occupants from coming into contact with the front panels or side structures at all, no matter how well designed. This is possible with both lap and shoulder belts such as are installed in the new cars. It has been estimated that 50 percent of the persons killed in automobile collisions would have survived had these restraints been used.⁶

Injury Reduction

The literature abounds with data on the injury reduction potential that is offered by lap and lap-shoulder restraints. Although one of the primary functions of the lap belt is to prevent ejection, it directs the upper torso and head to definite impact areas. The shoulder belt further reduces the consequences of flexing over the lap belt in crashes and decreases the possibility of head-face impacts. In a recent review of car crashes in which occupants were wearing seat belts and shoulder belts, a significant decrease was noted in the number and severity of body injuries in all types of collisions.¹⁵

Reports of occupant injuries purportedly from the lap seat belt have been appearing in the literature. Many of these individual reports add very little data to the general subject. They describe only the injury supposedly or actually attributable to the seat belt. Data are lacking on items useful to highway safety studies—occupants' location in the car, his height and weight, the make, model and year of the car, the type of impact and the like. To state that "the car hit a large tree at high speed" is meaningless. *Where* did the car hit—head-on? Front? Side? Rear? If nothing else, a photograph of the car would be useful, or a measurement of the crush damage. Without this information, our engineering colleagues cannot make use of the medical data.

From our experience, and that of other crash investigators, a properly worn lap belt will decrease the total body injury severity in the majority of collisions. With the shoulder belt also being worn, significant further decrease will be achieved.

We believe therefore that it behooves all physicians to be concerned in this aspect of public health and with the countermeasures of choice—the lap-shoulder belts. But how many physicians are knowledgeable enough to discuss the medical aspects of highway injury prevention with their patients? More individuals in the United States could probably be usefully instructed through the physician's office than by any of the mass media techniques. Because of the physician's unique relationship with his patient, he should diligently and seriously consider office procedures involving education of the patient toward lap-shoulder belts. A simple sign in the waiting room or a supply of informative

literature (brochures, pamphlets) available to patients would be most useful. In addition, the physician's own example of wearing the lap-shoulder belts whenever he and his family members drive is also a very worthwhile educational technique.

One of the problems is that the average physician does not have ready access to current information about traffic medicine except through the newspapers and an infrequent journal article. And one cannot expect a physician to read all of the varieties of journals in order to keep abreast of developments in this important health problem. He can simplify the task of keeping informed by perusal of the four or five publications that the American Association for Automotive Medicine puts out each year. These publications include information on all the fields of traffic medicine, including emergency medical care, alcohol and drugs, federal motor vehicle standards, medical aspects of driver licensure, and other useful data. A quick review of these informative items by the busy physician will keep him currently informed and provide him with pertinent information for ready use.

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Emergency Medical Care and Care Systems in California

Motor Vehicle Accidents

KENNETH E. DUFFEY, M.D., San Francisco

■ *Emergency Medical Care and Emergency Medical Care Systems are defined. The need for a distinction between the two is given. Motor vehicle accidents in 58 California counties are analyzed. The status of hospitals serving traffic trauma in California is given with respect to quality of care. The location of California hospitals with respect to the percent of motor vehicle trauma is shown. The importance of time lapse in emergency medical care systems and the reasons for time lapse errors is explored. The need for data processing and systems analysis in California emergency medical care systems is pointed out.*

EMERGENCY MEDICAL CARE of vehicular injury victims should be as broadly defined as possible. It should include everything that is done to or for the accident victim beginning from the time of his first discovery until he is either pronounced dead or has arrived and received definitive medical care of injury by a physician or team qualified to treat the injury in a hospital or emergency room environment appropriate to the degree of injury and to the requirements of the treating physician or team.

A broad definition of emergency medical care allows consideration for first-aid by laymen, police, paramedical, ambulance, and nursing personnel as well as general or specialty medical care administered to the victim.

Emergency medical care should be defined separately from emergency medical care systems. An emergency medical care system may be defined as the strategy and logistics used to implement emergency medical care. An emergency medical care system includes the location of facilities, personnel, methods of transportation, including ambulances, rescue vehicles, staffing of hospital emergency facilities, x-ray, laboratory, operating room, and intensive care facilities and their design and construction, on-site quarters for personnel, training and postgraduate education of paramedical and medical personnel, data collection, and systems analysis. It may include a traffic medicine research facility.

It is important to make the distinction between care and system because the physician who is directly responsible for emergency medi-

Reprint requests to: K. E. Duffey, M.D., 909 Hyde Street, San Francisco, Ca. 94109.

TABLE 1.—The Distribution of the Total Killed and Injured in Fifty-Eight California Counties in Auto Accidents in 1968 by County, Population Sizes and Totals, and the Percent Rate Per County/Population

<i>Population Group</i>	<i># Counties per group</i>	<i>Population of Total Group</i>	<i>Total # killed</i>	<i>Total # injured</i>	<i>Total # killed and injured</i>	<i>Percent killed and injured</i>
under 10,000	6	25,599	36	656	692	2.78
10-24,999	11	172,118	150	2,413	2,563	1.47
25-49,999	7	261,111	187	4,074	4,261	1.63
50-99,999	7	438,443	237	6,421	6,658	1.57
100-199,999	9	1,293,424	482	14,904	15,386	1.13
200-499,999	8	2,558,360	897	30,030	30,927	1.19
500-999,999	5	3,145,867	740	35,138	35,878	1.14
1,000,000	5	11,948,213	2,050	134,430	136,480	1.14
and over						
State Totals	58	19,873,125	4,779	218,066	222,845	1.25

cal care of the vehicular accident victim may not be directly responsible in the same way for the shortcomings of an emergency medical care system.

An attempt will be made to describe the scope of the vehicular accident death and injury problem in California and to describe some of the more important shortcomings in emergency medical care and emergency medical care systems in California.

Scope of the Problem

There are 58 counties in California comprising the socio-economic units and political sub-divisions in which vehicular accidents occur and are treated. They range from six mountainous and predominantly wilderness area counties each with a population under 10 thousand and accounting for a total of 36 killed and 656 injured in vehicular accidents in 1968 to five urban counties each with a population of one million or more in which a total of 2,050 killed and 134,430 vehicular accident injuries occurred in the same year.¹ The remainder of the counties consist of population groups as shown in Table 1 together with their total number of killed and injured. The smaller population groups are rural, the middle population groups are predominantly agricultural, and the larger population groups contain large metropolitan-suburban centers.^{1,2}

Table 1 shows a breakdown of the 58 counties and the percentage rate of killed and injured for each county population group. It is significant that the rate of killed and injured is two and a

half times greater in the smallest rural population group than in the two largest urban population groups. It is also significant that the percent rate of fatalities and injuries decreases as the population rises.

Reference to Table 1 and Table 2, which names the counties in California by population group, allows further identification and comparison of one group of counties with the others.^{1,2}

To add further perspective, consider that the nine counties in the 100,000-199,000 population group, while in the middle of the listed California population groups, are together larger in population than sixteen states in the nation, and consider further that Los Angeles County alone has a larger population than forty three states in the nation.³

The Big Fourteen Counties

Fourteen counties accounted for 83 percent of the total 244,797 persons killed and injured in California in 1968. The remaining 17 percent were killed and injured in the other 44 counties. Table 3 lists the 14 major counties. Of the total killed and injured in California, 40 percent were killed and injured in Los Angeles County and 43 percent in the other 13 major counties.

No correlation was found when total number of roadway miles by county was plotted against total number of accidents within the 14 counties.

Hospitals Serving Traffic Trauma

Four hundred fifty-nine California hospitals responding to a survey of emergency and disaster medical services conducted by the Cali-

TABLE 2.—The Counties in Each Population Group Are Shown According to the Figures of the CHA-CMA Survey (December, 1969)

<i>under 10,000</i>	<i>10-24,999</i>	<i>25-49,999</i>	<i>50-99,999</i>	<i>100-199,999</i>	<i>200-499,999</i>	<i>500-999,999</i>	<i>1,000,000 & over</i>
Alpine	Amador	El Dorado	Imperial	Butte	Fresno	Contra Costa	Alameda
Mariposa	Calaveras	Madera	Kings	Humboldt	Kern	Sacramento	Los Angeles
Modoc	Colusa	Nevada	Mendocino	Merced	Marin	San Bernardino	Orange
Mono	Del Norte	Siskiyou	Napa	San Luis Obispo	Monterey	San Francisco	San Diego
Sierra	Glenn	Sutter	Placer	Santa Cruz	Riverside	San Mateo	Santa Clara
Trinity	Inyo	Tehama	Shasta	Solano	San Joaquin		
	Lake	Yuba	Yolo	Sonoma	Santa Barbara		
	Lassen			Stanislaus	Ventura		
	Plumas			Tulare			
	San Benito						

TABLE 3.—The Fourteen California Counties Accounting for 93 Percent of the Total Number of Persons Killed and Injured in California. Population and Number of Registered Vehicles Are Shown. Number of Hospitals Responding to the C.M.A. Survey Providing 24-hour Emergency Service Is Shown

<i>Geographic Area and County</i>	<i>Population</i>	<i># Registered Vehicles</i>	<i># Killed in Auto Accidents</i>	<i># Injured in Auto Accidents</i>	<i># Hospitals in C.M.A. Survey</i>	<i># Hospitals with 24 hr. service</i>
Los Angeles	7,032,075	4,403,525	1,156	98,389	143	60
San Bernardino	684,072	427,314	284	8,533	16	3
San Diego	1,357,854	757,654	280	13,050	19	10
Orange	1,420,386	855,042	248	15,477	16	4
(Anaheim, Santa Ana)						
Alameda	1,073,184	645,746	216	11,147	19	10
Riverside	459,074	301,112	182	6,230	11	4
Kern	329,162	237,014	167	3,741	11	2
(Bakersfield)						
Fresno	413,053	279,139	153	5,233	10	1
Santa Clara	1,064,714	615,809	150	7,514	12	7
(San Jose)						
Sacramento	631,498	428,736	128	7,587	9	5
San Joaquin	290,208	197,900	125	3,882	7	2
(Stockton)						
Contra Costa	558,389	346,828	123	5,412	8	5
San Francisco	715,674	377,324	108	9,220	21	10
San Mateo	546,430	369,654	97	4,386	10	5

fornia Hospital Association and California Medical Association (CHA-CMA Survey)² in 1969 indicated participation in some form of service to the victims of vehicular trauma. The type of emergency care system service provided by these hospitals is shown by size of county in Table 4.²

If the availability of a physician on the hospital premises or 15 minutes away from the premises for emergency attendance of accident victims daily each 24 hours is used as a criterion for basic minimum quality of emergency care, then

114 surveyed hospitals which do not meet this standard would include those providing first aid with a registered nurse only available, those providing referral only, and those having no emergency room (refer to Table 4).

If the 114 hospitals are subtracted, there remain 345 hospitals in California which meet the criterion for basic minimum quality of emergency care as defined.

Of the 345 hospitals, 219 (63 percent) are located in the big 14 counties where 83 percent

TABLE 4.—The Number of Hospitals and Type of Emergency Service Offered by Responding Hospitals to a 1969 CHA-AMA Survey Shown by County Population Size in California

County Population Size	Type of Service and Number of Hospitals					Total
	24 hr. service with MD and RN	Standby 24 hr. with RN*	First Aid and Referral with RN	Referral Only	No. Emergency Room	
under 10,000	2	3	0	0	0	0
10-24,999	0	19	0	0	0	19
25-49,999	1	13	0	1	1	16
50-99,999	3	21	0	1	0	25
100-199,999	10	37	4	1	2	54
200-499,999	19	35	5	2	2	63
500-999,999	31	23	5	6	4	69
1 million and over	89	39	15	44	21	208
Totals	155	190	29	55	30	454

*"Standby 24 hr. with RN" is defined as having a registered nurse on duty in the emergency room each twenty-four hours and a physician available within fifteen minutes.

of the killed and injured from vehicular trauma occurs. In the remaining 44 counties, where 17 percent of the vehicular trauma occurs, 126 of these hospitals (37 percent of the total 345) are located. Seventy-nine hospitals (23 percent) are located in Los Angeles where, as stated earlier, 40 percent of the trauma in the state occurs.

Caution should be exercised in placing interpretations concerning quality of emergency care on these statistics beyond that already defined. It is probably valid to draw the conclusion that uniform high quality of care for all types of vehicular trauma does not exist in the 144 hospitals eliminated simply on the basis that no physician is present. No conclusions may be drawn, however, concerning quality in the 345 hospitals remaining. Within Los Angeles County, for example, institutions exist capable of providing highest quality of specialized care for extensively traumatized victims of vehicular injury. Neither this capability nor the capacity for numbers of cases treatable by such an institution is represented. Nevertheless such an institution ranks in the data along with the smaller hospital providing one 24-hour physician.

Furthermore, without an evaluation for capacity for care per institution, caution must be exercised also in concluding that an over-supply or under-supply of emergency care facilities exists within a given area.

A Generalization of Capacity

A generalized idea of capacity of the 345 hospitals may be obtained from the following listing

showing the percent of hospitals maintaining certain facilities (derived from CHA-CMA survey²).

Facility	Percent of Hospitals
clinical laboratory	100
operating rooms	100
x-ray equipment	100
electrocardiographs	100
pharmacy	84
pathology laboratory	71
intensive care units	61

Time and Distance Factors in Emergency Medical Care Systems

The primary function of an emergency ambulance, helicopter, or other type of rescue vehicle in an emergency medical care system is to reduce the time from the moment of trauma to the delivery of treatment. Whatever is done to reduce the time lapse with safety adds to the efficiency of an emergency care system.

It is within the area of the emergency delivery system that California physicians and hospitals have exercised careful discrimination between personal responsibility for the patient when they are in attendance and responsibility for the structure of the system designed to bring the patient for treatment.

A survey showed that 55 percent of California hospitals are reluctant to assume a responsibility for coordination of emergency medical care systems.²

Although a majority of California hospitals rated their local emergency rescue systems as

"good," important shortcomings in the systems were observed.² According to data in the CHA-CMA survey, 33 to 80 percent believed that communications systems between emergency vehicles and hospitals were inadequate; high percentages of hospitals also listed inadequately trained ambulance personnel, inadequate equipment, and strategically poor location of vehicles as shortcomings.

It may be concluded that each of these shortcomings is an error within the emergency care systems in California because each in some way contributes to a higher rather than lower time lapse from the moment of trauma to the delivery of treatment to the victim.

Frey,⁴ referring to studies done by the Department of Surgery at the University of Michigan Medical School, stated that physicians who care for the acutely injured have a responsibility to inform the public of the need to improve emergency medical care systems because they can best recognize deficiencies and appreciate the need for rapid transport, communications from ambulance to hospital, and trained specialty and paramedical personnel.

Frey implied that an informed public will lead to the correction of errors in emergency medical care systems. Public good-will is one important consideration, but other considerations exist in California also. A California State Legislature report recently surveyed in detail the reasons for failures in the emergency ambulance systems in California which appear to be predominantly economic.⁵

Physicians As Educators Within Emergency Medical Care Systems

Methods for reducing the time lapse and increasing the safety of victims of vehicular trauma by proper extrication of accident victims have been studied in depth.⁶ Training of paramedical personnel⁷ and standards for emergency ambulance services⁸ have been well developed. State and local Committees on Trauma of the American College of Surgeons may be consulted for training projects. A practical description of many problems solved by a highly efficient urban

emergency medical care system has been described by Waters.⁹

Need for Data-Processing and Systems Analysis

One reason for inertia in upgrading emergency medical care and emergency medical care systems in California is the lack of central data processing and systems analysis.

Retrospective analysis of the variables in individual systems is of little use in the decision-making process. What is needed is a data base from which data by type may be extracted. Data is currently needed on:

- Time lapse from discovery of accident to arrival of emergency vehicle
- Victim dead at scene of accident
- Victim dead on arrival at emergency hospital
- Time of death after arrival
- Distance traveled from accident to first emergency treatment stop
- Second stop if any
- Time lapse from leaving accident to first emergency stop. To second stop.
- Specialty care available at any potential emergency care stop.
- Paramedical treatment if any
- Severity of tissue damage

When this data is made available, more effective analysis of emergency medical care systems in California may be undertaken.

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Emergency Medical Transportation

A Survey of California Ambulance Operations

IRMA M. WEST, M.D., C. EARL GETTINGER, JR., DOROTHY MEYER,
MICHAEL ROSENTHAL, RICHARD SNOW, FLORENCE R. WEINER, R.N.,
AND LE MAR W. HOAGLIN, *Berkeley*

■ *The most urgent recommendation expressed by physicians, Red Cross officials, ambulance operators and others polled in this ambulance survey was to make much more emergency medical care training available to ambulance personnel. Very few sick and injured receive first aid before an ambulance arrives. Therefore there is also an urgent need to train and motivate the public to provide first aid at the scene of the emergency. Urban ambulances usually respond within 10 minutes, but often rural ambulances take more than 30 minutes to reach an emergency. It is during this interim that lives which could be saved by prompt first aid are lost. Little use has been made of aircraft as emergency ambulances; in 1968, only one emergency trip in 1500 was made by helicopter. Also, California has fewer ambulances which make fewer emergency trips on a population basis than the country at large.*

Communications at all levels need attention. Seventy-eight percent of the ambulance operations serving the public are not listed among the emergency numbers on the inside front page of telephone directories. Less than ten percent of ambulances have direct radio communication with hospitals.

In California most ambulance services are commercially operated and there are formidable financial problems which must be solved before these services can be brought into place as a part of the emergency medical care system.

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Reprint requests to: I. M. West, M.D., Bureau of Adult Health and Chronic Diseases, State Department of Public Health, 2151 Berkeley Way, Berkeley, Ca. 94704.

A STATEWIDE SURVEY OF CALIFORNIA Ambulance Operations was undertaken to gather basic data about the number, distribution, level of service, and other characteristics pertinent to ambulance services in California—information which never before had been available for the state as a whole. The survey was necessary to plan for

TABLE 1.—*Ambulance Services and Ambulances by Type of Ambulance Service, Ratio of Ambulances to Service, California, 1969*

Ownership of Ambulance Service	Services or Operators		Ambulances		Number Ambulances per Company or Service
	Number	Percent	Number	Percent	
Total	535	100	1,557	100	2.9
<i>Serving Public*</i>					
Commercial	177	33	602	39	3.4
Funeral director	36	7	124	8	3.4
Private or nonprofit hospital	8	1	15	1	1.9
Local tax supported hospital	13	2	53	3	4.1
Volunteer fire department	25	5	33	2	1.3
Municipal, district or other regular fire department	37	7	65	4	1.8
Police department	7	1	24	2	3.4
Voluntary organizations	14	3	15	1	1.1
Other local government services and miscellaneous	14	3	57	4	4.1
<i>Serving Special Groups**</i>					
Industrial	62	12	88	6	1.4
Military	92	17	401	26	4.4
State government	26	5	35	2	1.3
Federal—nonmilitary	13	2	29	2	2.2
Other	11	2	16	1	1.5

Source: Ambulance Survey, California Department of Public Health, 1969.

*Sixty-two percent of the ambulance operations serve the general public. Sixty-three percent of the ground ambulances in California serve the general public.

**Two hundred and four or 38 percent of the ambulance operations serve special groups. Five hundred and sixty-nine or 37 percent of the ambulances in California serve only special groups.

compliance with the Federal Highway Safety Standard for Emergency Medical Care for Traffic Accident Victims. This standard requires a state program in cooperation with local political subdivisions to ensure that persons involved in highway accidents receive prompt emergency medical care. The survey, begun in 1968 and completed in 1970, was conducted by the California State Department of Public Health through an agreement with the State Business and Transportation Agency with funding assistance from the National Highway Safety Bureau.

The principal source of data was a questionnaire mailed to all ambulance operations; 95 percent responded, thereby providing comprehensive statewide data. A special study of air ambulance operations was carried out primarily by personal interview. Additional data were collected from emergency room physicians, California Highway Patrol Area Commanders and local chapters of the American National Red Cross by mailed questionnaires. Other studies were made on the following subjects: ambulance accidents, local ambulance ordinances, legal problems in ambulance operations, and work

injuries of ambulance personnel. For these, data were collected from county Emergency Medical Care committees, court and other legal records, and the Bureau of Labor Statistics and Research of the State Department of Industrial Relations. The full report covers almost 500 pages. This article is a short summary.

The survey produced a number of unexpected findings and provided data to confirm and sometimes question widely-held opinions of knowledgeable persons in the field of emergency medical transportation.

An unexpected finding was the number of ambulance services, companies or operations in the state—612 ground ambulance and 88 air ambulance services. They exceeded previous estimates by a considerable margin. Also unexpected was the large proportion of ambulance operations (38 percent) serving special groups such as military and industry, but not the general public. Another surprising finding was the small proportion of services for the public which are operated by tax-supported agencies such as fire and police departments (20 percent). Most ambulance operations available to the California

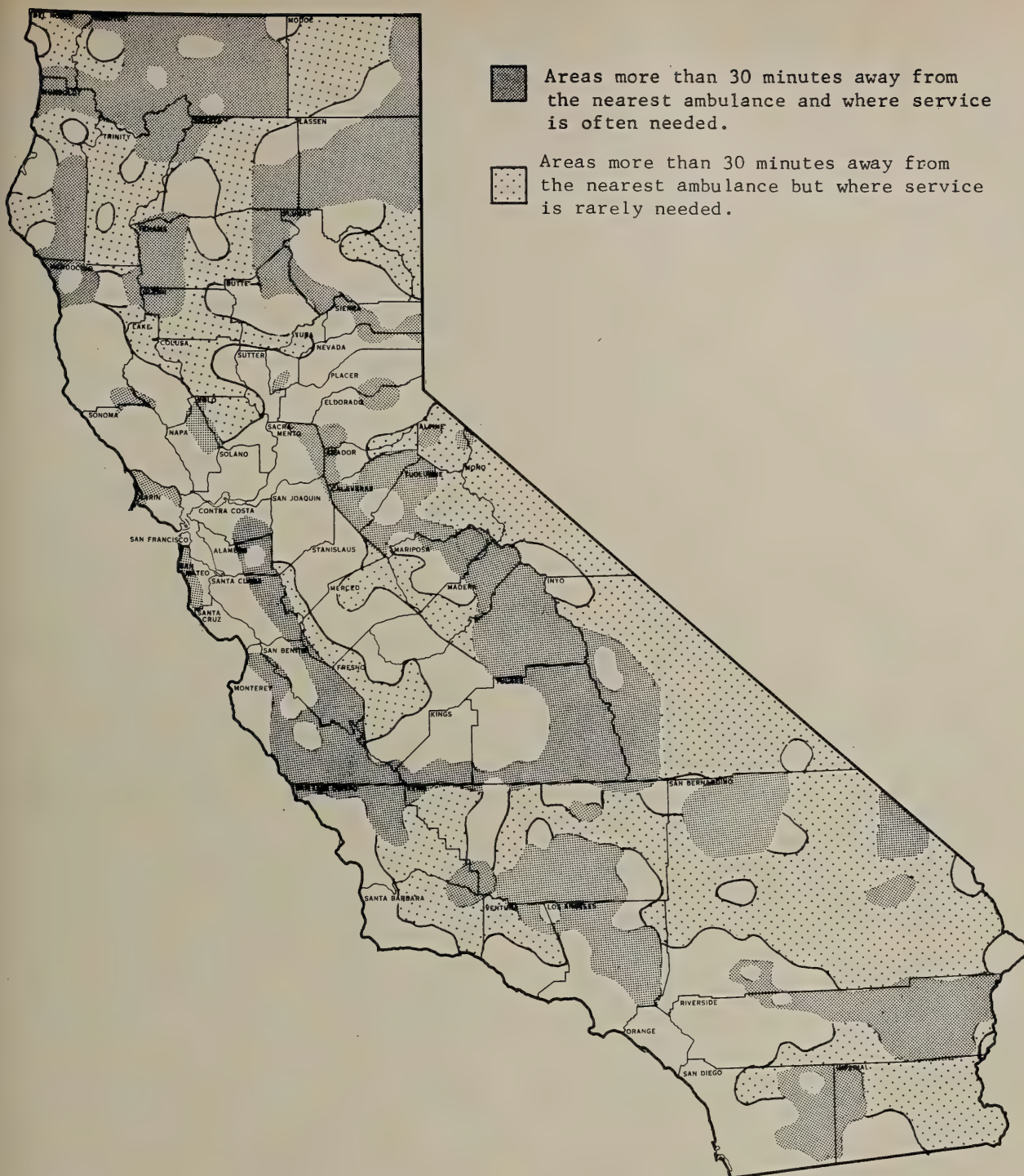


Figure 1.—Areas designated by ambulance operators and/or California Highway Patrol as being more than 30 minutes from some ground ambulance service.

public come from commercial operations, (65 percent); very few are from funeral homes (11 percent). (See Table 1.)

A significant finding was that medical emergencies occurring within about one-fourth of the California's geographic area are over 30 minutes

away from the nearest ground ambulance. Not included in this estimate are unpopulated areas without traffic where there is little need for service (Figure 1).

Perhaps not unexpected is the fact that most ambulance personnel (68 percent) are part-time

TABLE 2.—*Ambulance Personnel by Type of Ambulance Service, California, 1969*

<i>Ownership of Ambulance Service</i>	<i>Ambulance Personnel</i>					
	<i>Total</i>		<i>Full-Time</i>		<i>Part-Time</i>	
	<i>Number</i>	<i>Percent</i>	<i>Number</i>	<i>Percent</i>	<i>Number</i>	<i>Percent</i>
Total	8,196	100	2,619	100	5,577	100
<i>Serving Public</i>	5,046	62	1,824	70	3,222	58
Commercial	1,966	24	1,154	44	812	15
Funeral Director	277	3	138	5	139	2
Private or nonprofit hospital	33	a	10	a	23	a
Local tax supported hospital	192	2	126	5	66	1
Volunteer fire department	446	5	4	a	442	8
Municipal, district or other regular fire department	817	10	192	7	625	11
Police department	740	9	6	a	734	13
Voluntary organizations	202	2	1	a	201	4
Other local government services and miscellaneous	373	5	193	7	180	3
<i>Serving Special Groups</i>	3,150	38	795	30	2,355	42
Industrial	1,077	13	123	5	954	17
Military	1,672	20	617	24	1,055	19
State government	239	3	23	1	216	4
Federal—nonmilitary	97	1	13	a	84	2
Other	65	1	19	1	46	1

^aLess than 1 percent.

Source: Ambulance Survey, California Department of Public Health, 1969.

workers and 23 percent of the part-time workers are volunteers. As the population decreases, the proportion of volunteers increases until in rural areas over half of all ambulance personnel are part-time volunteers. The number of ambulance drivers and attendants reported was 8,196. Of the total, 5,577 worked part-time, and 1,266 of the part-time personnel were volunteers (Table 2). Commercial operators employed the largest proportion of full-time personnel. Full-time salaries ranged from a low of \$300 to a high of \$900 a month, the higher salaries being paid in metropolitan areas. Almost half of the full-time workers had been employed for less than two years. Turnover is high. Part-time workers had worked longer and had much less turnover.

Practically no courses in driving emergency vehicles are provided for ambulance drivers. About 40 percent of them are not required to have a state ambulance drivers' license, usually because they operate on government or private property or are police or firemen.

First-aid training is provided almost entirely by the American National Red Cross; very few personnel attend other courses offered. Two out of three ambulance operators believe that the advanced Red Cross first-aid course, although

excellent basic training for the public, is inadequate for ambulance personnel. They also favor a state licensing program in emergency medical training for ambulance personnel. They favor medically controlled training—not training directed by non-medical educational institutions.

The military has an outstanding record in the survival of injured for whom they provide emergency care and transportation; therefore comparisons were made between it and the civilian ambulance system in California. The most notable difference was in the paramedical training for civilian ambulance personnel. Only about 19 percent of the full-time civilian ambulance personnel and only 7 percent of the part-time had paramedical training, while 85 percent of the military did. Another difference was the military's large proportion of truck and van ambulances which have sufficient room to provide life-saving services. Also different was communications. The military were more likely to have direct radio communication with hospitals than were civilian ambulances.

Injured or ill persons seldom receive first aid before an ambulance arrives. If first aid is provided, law enforcement officers are the most likely providers. With respect to lifesaving emer-

TABLE 3.—Emergency Trips and Traffic Accident and Dry Run Trips Which Were for Emergencies, by Type of Ambulance Service, California, 1969

Ownership of Ambulance Service	Total Trips	Emergency Trips		
		All Emergency Trips	Traffic Victim Trips	Dry Runs
Total	849,209	361,692	120,906	39,113
<i>Serving Public</i>	743,182	338,577	118,353	35,915
Commercial	484,555	187,961	71,983	19,440
Funeral director	32,619	10,470	3,786	993
Nonprofit or private hospital	3,474	1,214	473	60
Local tax supported hospital	49,891	1,448	497	67
Volunteer fire department	3,322	2,023	989	133
Municipal, district or other regular fire department	30,001	19,672	5,142	1,547
Police department	25,998	25,951	7,095	10,347
Voluntary organizations	1,666	1,247	663	64
Other local government agencies or services	111,656	88,591	27,725	3,264
<i>Serving Special Groups</i>	106,027	23,115	2,553	3,198
Industrial	7,798	4,607	108	114
Military	75,716	15,565	2,244	2,913
State government	16,876	2,476	73	141
Federal—nonmilitary	869	201	79	18
Other	4,768	266	49	12

Source: Ambulance Survey, California Department of Public Health, 1969.

gency first aid, this interval can be the most critical and can be filled only by providing every citizen with first-aid training and the incentive to use it.

Communication Equipment

Much is to be desired in communications equipment and systems. More than half of the operators do not always notify hospitals of the impending arrival of emergency patients. Some cannot for lack of radios; others find it serves no purpose. Less than 10 percent of the commercial services have direct radio communications with hospitals, while 28 percent of the military do. Eighty-seven percent of the ambulances serving the general public, but only 52 percent of the vehicles serving special groups, have two-way radios at their headquarters. About 44 percent of the operations serving the public report ineffective or difficult radio communication in some parts of the area served. Only one county has a coordinated communication system with central command and control, and central receiving and dispatch, for all public emergency services including ambulances.

In the forefront of rapidly developing ambu-

lance communications are monitoring systems which transmit vital signs from ambulance patients to the emergency room during the trip to the hospital. These systems are demonstrating lifesaving capabilities for acute heart emergencies. They are in operation in Belfast, Moscow and New York. Pilot programs of this type are now in operation in Los Angeles and soon may be in San Francisco.

Seventy-eight percent of the ambulance operations serving the public are not listed among the emergency numbers on the inside front page of telephone directories. Thirteen percent of the operators serving the public are not listed anywhere in the telephone directory. The proposed Universal Emergency Number 911 was not in operation anywhere in the state at the time of the survey although it was under consideration in several cities.

In California for 1968 about 46 percent of the total number of ambulance trips (almost 850,000) for the public were emergencies (Table 3). According to one report, the national average for emergency trips is 15 percent of the total. According to another report it is 33 percent. Apparently, in California a higher proportion of

ambulance trips are reported as emergencies than elsewhere in the country. However, the ratio of emergency trips to population is only half the national average of one emergency trip each day for each 10,000 population. In California in 1968, the ratio was one emergency trip a day for each 20,000 population. This apparent underutilization of ambulance services is substantiated by the fact that California has only six percent of the nation's ambulances. The expected number would be closer to ten percent because approximately ten percent of the population lives in California.

Traffic accident victims accounted for 14 percent of the total trips and 33 percent of the emergency trips. Commercial ambulance operators made the most trips of all kinds. In rural areas thirty-two percent of the emergency trips were for non-residents while in metropolitan areas only five percent were for non-residents.

One thousand five hundred and fifty-seven ambulances were reported by the 535 operators surveyed. The 331 operations serving the public reported 988 ambulances. The ratio of vehicles serving the public to population is about one ambulance for every 20,000 population and one service for about 60,000 population. About half of the ambulances operating in the state are over four years old. Only about half have sufficient height or head room to allow certain life-saving services to be provided.

Ambulances serving the public use the red light and siren for the right-of-way and privilege of exceeding the speed limit to the scene of an emergency most of the time. However, once the patient is on board, the red light and siren are not used most of the time. A significant majority of operators are not in favor of discontinuing the red light and siren and its attendant privileges for California ambulances. The "usual" response time for metropolitan and city ambulances to reach the scene of an emergency is ten minutes or less, with about the same time to transport the patient to the hospital. The response time is longer and too variable to be estimated for rural areas.

Nine out of ten operators serving the public always have both an attendant and a driver on ambulances responding to emergency calls, and almost 90 percent favor a law requiring both. (The present law requires only a driver but steps are being taken to require both.)

Saturday is the busiest day, 3 p.m. to 6 p.m. the busiest hours, and summer the busiest season for most ambulance services.

Financial problems overshadow all others as far as most commercial ambulance operators are concerned. Of operators who charge for services, fewer make a profit than break even or show a loss. Most commercial operators have some other business, and without its financial assistance many could not operate. Collections vary widely and delays and "red tape" for charges collected pose additional expense. Half of the ambulance services make fewer than 600 trips annually, although more than three times that number is considered minimum to support one full-time ambulance. Commercial services average just over three ambulances each. It is clear from data that ambulance operations need greater financial assistance if they are expected to raise their standards of service or to comply with any additional legal requirements. It is also clear that government agencies must assume greater responsibility for providing ambulance services where it is needed, but unavailable or too far away.

Equipment for First Aid

Over 500 ambulance operators rated 47 pieces of first aid equipment and supplies which have been most often included on recommended or required lists of minimal equipment for ambulances. Two-thirds of the operators agreed on 21 items as essential. These items in rank order are: flashlight, portable stretcher, portable oxygen and breathing equipment, dressings and compresses of assorted sizes, ambulance cot, clean linens, pillow, universal dressings, emesis basin, adhesive, suction equipment, mouth-to-mouth airways, transparent oxygen mask, triangular bandages, tourniquets, roller bandages, oropharyngeal airways, towels, wool blanket, oxygen driven resuscitator and aspiration bulb. Not included as essential by two-thirds of the operators were splints, safety pins, spine boards, and bag and mask resuscitators, all of which appear on the American College of Surgeons' list of minimal equipment for ambulances. Also absent among items judged essential by two-thirds of the operators were four items on the list of equipment required by the ambulance regulations of the California State Highway Pa-

trol. They are: splints, bag and mask resuscitators, sandbags and hemostats.

Ninety-two California physicians, selected for their expertise in emergency medical care, rated the same list as was rated by ambulance operators. Of the 47 items, 23 were rated essential by two-thirds of the physicians. Of these 23 items, 16 had been rated as essential by two-thirds of the ambulance operators. The 23 items considered essential by the physicians in the order rated were: flashlight, oropharyngeal airways, portable oxygen and breathing equipment, universal or large dressings, suction equipment, adhesive tape, bag resuscitator and mask, portable stretcher, ambulance cot, non-porous dressings, dressings and compresses of assorted sizes, mouth-to-mouth resuscitation airways, transparent oxygen masks, aspiration bulb, emesis basin, clean linens, tourniquets, spine boards, pillow, safety pins, kerlex roller bandage, extrication tools, and blood pressure cuff. Missing from this list were splints and triangular bandages which appear on the American College of Surgeons' list. Also missing were splints, triangular bandages, towels, blankets, gauze roller bandages, sandbags, and hemostats which appear on the list of required equipment for ambulances in the California State Highway Patrol regulations. (Bandage shears were inadvertently omitted from the list of 47 items. They probably would have rated high.)

A number of physicians pointed up the disproportionate emphasis placed on ambulance "hardware" when training of personnel who use the equipment should be the prime consideration.

Of the 47 items there was agreement on only seven among four groups, namely two-thirds of the California operators, two-thirds of a selected group of California emergency room physicians, the American College of Surgeons (through its list of minimal equipment) and the California Highway Patrol (through its list of equipment required on California ambulances). These seven items were: portable oxygen and its breathing equipment, transparent oxygen masks, dressings and compresses, adhesive, pillow, suction equipment and mouth-to-mouth airways.

The most unexpected result of the equipment survey was the relatively low regard in which splints were held by both operators and physicians. Considering that surgeons and orthoped-

ists highly recommended padded board splints and hinged half-ring splints, this result was puzzling, considering a study of ambulance trips made in California in 1963¹ in which it was observed that the most frequently noted omission of ambulance personnel was neglecting to splint fractures, particularly those of the femur where bleeding can occur in massive amounts. The traction half-ring splint, unpopular with California ambulance operators, is most often recommended for femur fractures.

Another point of interest is the relatively low regard by operators for the bag and mask resuscitator, this item ranking 24 on a list of 47 pieces of equipment. Nevertheless, 60 percent of the operators did consider it necessary. This item is the only piece of equipment that the California legislature has by law demanded be present on ambulances.²

Training in Emergency Care Needed

However, by far the greatest concern of physicians expert in emergency medical care is lack of emergency medical training for ambulance personnel. These physicians favor a state licensing program for drivers and attendants on all ambulances responding to emergencies. They also favored retaining the emergency vehicle status of ambulances with red light and siren. Of physicians who are acquainted with California's ambulance regulations, more were dissatisfied than satisfied with them, primarily because training requirements are considered inadequate.

Among the most popular recommendations were:

1. Rural ambulance services must receive state subsidy,
2. Emergency medical communication systems must be improved throughout the state,
3. All medical transportation should be regulated, including wheelchair cars, non-emergency transfers and air ambulance services, and
4. A statewide program to coordinate, organize, and subsidize all emergency medical transportation and emergency hospital services.

Eighty commercial air ambulance services were identified. The commercial companies maintain 161 fixed-wing aircraft and 41 helicopters. A large majority of the aircraft, in addition to serv-

ing as air ambulances, are used in other work. In 1968, a total of 1,432 patients were transported, of whom only 236 were emergencies carried by helicopter. Fifty percent of them were carried by three operators. About one in every 1,500 emergency ambulance trips was by helicopter in 1968. Most aircraft carry one patient and variable first aid equipment. There are no regulations covering the ambulance aspects of air service.

Ambulance ordinances or contracts were identified and collected for 19 or one-third of California's counties and 23, or six percent, of its 404 cities. Nineteen of the cities and 12 of the counties through either ordinances or contracts required both a driver and an attendant on each emergency ambulance. Two counties and seven cities required that both driver and attendant have a current advanced Red Cross First-Aid Certificate. Most cities and counties with regulations delegated responsibility for enforcement to their health or police agency.

Ambulance Collisions

Although the number of traffic accidents in general has increased considerably since 1963, the number of ambulance accidents has not. There is, however, a significantly higher proportion of injury-producing collisions between ambulances and other vehicles at intersections than between other vehicles. During the first nine months of 1969, 84 ambulance accidents were reported, 56 of which involved injuries and fatalities. Four persons were killed and 116 injured in these accidents. Eighteen of the injured were patients in ambulances. About the same number of accidents occurred going to as leaving the scene of an emergency. Red light and siren were in operation in over half of all of accidents. In 27 percent of the accidents the ambulance driver received a citation. In 66 percent of the accidents involving another vehicle the other driver was cited, most often for failure to yield to an emergency vehicle. During the nine-month study period ambulance accidents occurred most often on Friday between 3 p.m. and 6 p.m.

All of the area commanders for the California Highway Patrol (CHP) responded to a questionnaire about ambulance services for traffic accident victims. The CHP investigates all traffic accidents involving death or injury on freeways and roadways in unincorporated areas of

California, and it places calls for almost 11,000 ambulance services annually. The CHP is responsible for regulation of ambulance services. It reported reasonable satisfaction with services in most locations throughout the state; however, there were serious problems in some areas because ambulance services were too distant. In about ten percent of the CHP areas some improper practices in extricating accident victims from wrecked vehicles were noted. The CHP also noted that traffic accident victims infrequently receive first-aid care before they or the ambulance arrive.

Ambulance operators and their employees expressed considerable concern about legal liability or suits involving patient care. Since this fear was reported to have an inhibiting effect on providing first aid services, an investigation of appellate court records was made to determine what facts were available. It was determined that the risk of legal action because of negligence taken against ambulance personnel, lay persons or even professional persons providing first aid or emergency care was remarkably low. As far as could be determined, traffic accidents, delays in reaching or delivering patients to the hospital, and patients slipping from cots or gurneys cover most of the reasons for suits brought against ambulance personnel. No suits concerned emergency medical care as such.

Judging from other surveys, California is remarkably different from other states in both its pattern of ownership of ambulance services and in their utilization. There are also pronounced differences within California between metropolitan and rural areas, particularly with respect to ownership of ambulance services, their availability, their personnel, extent of financial problems, communications, and response time.

A number of recommendations were made to assist the State and its local jurisdictions to correct those deficiencies in ambulance services where they were not in compliance with Federal Highway Safety Standards for Emergency Medical Care. The most important concerned making available throughout the state adequate emergency medical training for ambulance personnel and adequate first-aid training for every high school student. Also important was assigning legal responsibility to all local jurisdictions to provide ambulance services in compliance with standards of availability and quality of

service to be set by the State. Some form of financial assistance to ambulance operators also seemed urgent — particularly when increased training of personnel and availability of service are expected.

One of the most neglected aspects of ambulance service is communications. There is almost across-the-board lack of realization about the lifesaving potential and the opportunities for a more economic use of emergency services offered by modern communications. Each county should have such a system geared to its needs but also coordinated by a statewide network to deal with emergencies crossing county lines or covering several counties.

Emergency Call Listing Needed

Practically no help or information is given to the public about calling an ambulance in an emergency. Very few telephone directories provide an ambulance number among the front page emergency numbers. There is no single number designated or in use for the public to report an emergency, and a coin is usually needed for pay phones. Calls for ambulances may be relayed through several operators and agencies, thus increasing chances of error in the message. This survey documents the almost routine use of "Code 3" by ambulances to the scene (red light, siren, speed above limits, taking right of way) without knowing whether the situation

warrants it. A good communications system with a trained dispatcher could, in some situations, obtain and forward information to the ambulance driver which could reduce unnecessary "Code 3" trips to the emergency.

Ambulance accidents could be reduced by requiring that ambulances either obey traffic signals at all intersections or be provided with equipment to change intersection traffic signals in their favor.

Most of the recommendations were directed toward bringing ambulance services into the medical care field. The delivery of medical care has been designated as the nation's most urgent health problem. Ambulance operations have been one of the most neglected segments of medical care services. There have been advances in emergency medical care which can be brought to the ill and injured to save their lives. If immediate care and medical transportation services are to include these advances they must be brought into the paramedical field. Ambulances can no longer be considered as merely transportation, but must take their rightful place as an essential component of the emergency medical care system.

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CAR CRASHES FROM CAROTID KINKING CAUSED BY CRANING

Five of my patients had car wrecks when they turned their head while driving. In each I subsequently demonstrated a kinked internal carotid artery. One of the patients has had two wrecks. Another three patients with kinks bowed their head in church and had hemiparesis. On an arteriogram, with the head in an extended position the artery was open; with the head in a flexed position with the needle still in place, the vessel almost kinked off flow.

I nearly had a disaster once in testing one of the car wreck patients. He was sitting across from my desk and I said, "Hold your head down." He did—and fell over onto the floor. Now I ask any patient with transient symptoms to hold his head in extended, flexed, and rotated positions for 30 to 45 seconds to see whether I can reproduce symptoms suggesting some sort of angulation that might be causing reduced flow. Then to try to prove it with arteriograms, I have to get the head in that same position.

—E. STANLEY CRAWFORD, M.D., Houston
Extracted from *Audio-Digest Surgery*, Vol. 18, No. 11, in the Audio-Digest Foundation's subscription series of tape-recorded programs. For subscription information: 1930 Wilshire Blvd., Suite 700, Los Angeles, Ca. 90057.

MEDICAL STAFF CONFERENCE

Methadone Treatment of Opiate Addiction

These discussions are selected from the weekly staff conferences in the Department of Medicine, University of California, San Francisco. Taken from transcriptions, they are prepared by Drs. Sydney E. Salmon and Robert W. Schrier, Assistant Professors of Medicine, under the direction of Dr. Lloyd H. Smith, Jr., Professor of Medicine and Chairman of the Department of Medicine. Requests for reprints should be sent to the Department of Medicine, University of California, San Francisco, San Francisco, Ca. 94122.

DR. SMITH:* We are fortunate to have Dr. Barry Ramer, Director of San Francisco Community Mental Health Services Center for Special Problems, to speak to us today about opiate addiction and its treatment with methadone.

DR. RAMER:† The communication media have focused considerable public attention on the problems of narcotic addiction, which has emerged from the criminal domain to become one of society's major social and medical concerns. Since drug abuse and narcotic addiction are woven into our social fabric, it is important to understand the origins of narcotic addiction in the United States.

Opium was introduced into California by the Chinese immigrant population in the mid-nineteenth century. This poor and disenfranchised ethnic group of laborers utilized opium, at least partially, as a pharmacological escape from the monotony of their despairing existence. Opium "dens" were abundant in San Francisco until the closing of the Barbary Coast. Simultaneously in the East, with the introduction of the hypodermic syringe, morphine was injudiciously prescribed during the Civil War; and by the time that conflict ended thousands of soldiers, civilians, nurses,

and physicians were addicted. By the turn of the century, several hundred thousand Americans were using large quantities of opium and its alkaloids. Many patent medicines were substantially laced with large amounts of opium as the major ingredient. These drugs were found to have the unique qualities of reducing pain, producing narcosis and diminishing emotional turmoil. To the benefit of the distributor, they had the unique side effect of producing decided physiological and psychological dependence, thus assuring a steady and growing market.

At the turn of the century, several lay organizations began to press for control of drug abuse. They recommended sweeping reforms in legislation regarding alcohol and addictive drugs. This small but vocal minority pressed their will and obtained passage of bills prohibiting alcohol consumption and curtailing most narcotic usage. The American Medical Association fought vigorously against law enforcement's encroachment into the medical field. In spite of their efforts against infringements upon medical practice, the Harrison Narcotics Act was passed in 1914. During the succeeding years, the Act was enforced stringently, and by 1925 treatment of the addict was totally wrested from the medical community and was made solely a law enforcement concern.²

In 1935 the Federal Government opened the

*Lloyd H. Smith, Jr., M.D., Professor and Chairman, Department of Medicine.

†Barry S. Ramer, M.D., Assistant Clinical Professor of Psychiatry and Ambulatory and Community Medicine.

first prison hospital for the treatment of addicts at Lexington, Kentucky. Shortly thereafter a second institution was opened at Fort Worth, Texas. The populations in these treatment facilities were mainly Caucasians of the lower socioeconomic group. The practicing medical community was little concerned with the treatment of these "undesirables." Because the mere possession of heroin in the United States was made a felony, legitimate sources of this drug disappeared. Organized crime that was actively engaged in illegitimate alcohol production and importation found a new and lucrative market in the distribution of narcotics. With the repeal of Prohibition, these organized criminal syndicates began wide-scale distribution of narcotics in the ghetto communities throughout the United States. Once again, narcotics were utilized by the poor and oppressed as an escape from their bleak existence.

Substantial propaganda emanated from Washington warning of the horrors in narcotic addiction. During the 1930's and 1940's in numerous movies Hollywood stereotyped the addict and the criminal element associated with narcotic distribution. As long as narcotic addiction remained a ghetto problem, little concern was expressed by the middle class in the United States. Finally, in 1955 medical conscience was aroused. The New York Academy of Medicine expressed shock regarding the inhumane treatment of addicts in New York's state prisons.³ This prestigious group brought pressure on the New York state legislature to revamp the legal system there and proposed a civil commitment law whereby addicts could receive medical treatment for their addiction. At last, organized medicine was re-assuming its responsibilities to deliver treatment to narcotic addicts.

During the early 1960's, a new social awareness and concern was expressed regarding the plight of the addicted. Self-help movements, spearheaded by Synanon, began reexamining the treatment of the addicts. The public was made cognizant that a serious medical problem was responsible for a substantial portion of street crime.

Treatment Failures

During the 25 years of their operation, the federal facilities at Lexington and Fort Worth had little success in curing addicts. The treat-

ment relied solely upon total abstinence or incarceration, or both. Their rate of recidivism exceeded 90 percent.^{4,5} Clearly, these facilities were treatment disasters. In 1966, Congress passed the Narcotics Addict Rehabilitation Act (NARA) in an attempt to salvage these programs. The act provided for short-term inpatient treatment followed by extensive, long-range outpatient follow-up care. Unfortunately, results of the NARA program have been poor.⁶ Thousands of other addicts were sent to prison for rehabilitation, but few made any recovery.⁷ All attempts at incarceration and coercion met with failure.

The British have an entirely different philosophy regarding addicts, and much can be learned from them about humane treatment.⁸ They maintain that if addicts need heroin, then heroin should be made available to them under prescription. Unfortunately, some injudicious physicians there issued prescriptions indiscriminately; and, as a result, heroin was diverted illegally and created new addicts. Treatment control was then placed in the hands of a few reliable physicians and clinics. Private physicians in England can no longer prescribe narcotics for addicts. The British feel they are making substantial gains in controlling narcotic addiction without resort to incarceration.

The Addict Personality

Addiction has been described as a symptom of underlying psychiatric disorder. Despite years of study, efforts to identify the underlying disorder and provide treatment for it have yielded little success. It appears that there are as many reasons for people becoming addicts as there are addicts. The young ghetto resident, living under adverse conditions, perceives narcotics as the only escape from his environment and thinks that by "pushing dope" he possibly can achieve the material wealth necessary to graduate from the ghetto. On the other hand, the middle-class youth, with all material advantages, finds himself in conflict with his parents' ideals. His efforts to achieve individual identity plunge him into adolescent turmoil. Often on the verge of serious psychiatric disorder, he finds that narcotics diminish his feelings of anxiety, hostility and rage.

Traditional psychiatry has provided very few answers in the treatment of the addict. Many psychiatric texts deal at length with "the addict

personality," but swiftly discharge the matter of treatment as extremely difficult, yielding poor results.

Narcotics diminish primal impulses, including hunger, pain, aggression and sexual drive,⁹ while alcohol liberates aggressive, violent feelings and heightens sexuality. Narcotic addicts appear to have significant problems controlling their aggression and sexuality and use drugs to narcotize primitive brain centers responsible for mediating their primal drives. As a hypothesis, we may assume that the peace-conscious youth of today are repelled by war and aggression. They do not favor the use of alcohol, the drug of the older generation, which liberates hostile and aggressive behavior; rather they use narcotics, attempting to produce an inner peace and tranquility. These same youths, however, have given little consideration to the debilitating side effects and physical dependence associated with narcotic abuse.

Methadone Maintenance

During the past ten years, methadone maintenance has become one of the most widely accepted means of treatment available in the rehabilitation of narcotic addicts. Hundreds of programs now exist in the United States and the Western World. Results have been good: more than 80 percent of unselected patients remain free of narcotics other than methadone. Most have resumed productive lives and can be considered socially rehabilitated. Although it is true that daily methadone administration must be continued, physicians who carry out this treatment point out that in other medical fields maintenance doses of drugs are administered regularly for long periods to allay the symptoms of chronic conditions.

Methadone appears to have several pharmacological advantages over other drugs. Addicts who have switched to methadone maintenance experience no physical withdrawal syndrome. When given in daily maintenance doses, methadone produces no euphoria or sedation. It may be administered by mouth, and a single dose may have persistent pharmacological effects for 36 to 48 hours. Furthermore, the addict builds cross-tolerance to other opiate alkaloids. Once an addict has reached the maintenance level of methadone, other narcotics have no discernible psychological effect on him. Hence, the drug

TABLE 1.—Statistics on 249 Patients Admitted to CSP Methadone Maintenance Program July 9, 1969-June 30, 1971

	Range	Median	Mean
Age (years)	20-69	34	35.4
Education (years)	3-18	10	10.9
Heroin Addiction (years)	1-47	13	13.9
Duration Methadone Maintenance (weeks)	1-102	25	26
Length of Time in Prison (years)	0.1-20	3	4.5

appears to block the effects of other narcotics. Methadone also suppresses drug hunger and allows the addict to control an otherwise insatiable desire for illicit opium alkaloids.

San Francisco Experience

The San Francisco Department of Public Health Community Mental Health Services instituted a methadone maintenance treatment program in July, 1969, at the Center for Special Problems (CSP). At that time, methadone maintenance was an untried treatment method in California. The initial program was limited to a pilot study of 20 patients who were older, long-term recidivistic addict-felons who had had numerous failures in other treatment settings. The maintenance program showed remarkable success with this unpromising group of heroin addicts, and expansion of the CSP program became possible. Even though there have been many administrative and clinical problems entailed in rapid expansion of the program (the present number of addicts in treatment is 400) the treatment results are still heartening.

Table 1 summarizes selected data describing admissions to the program during its first two years of operation. All patients who consumed at least one dose of methadone are included in these figures. Although it may seem questionable to count patients who receive just one or two doses of methadone as being "treated," this reporting is necessary so that our data may be compared with data on other treatment programs. Of the 249 addicts who were admitted to the methadone maintenance program between July 9 1969 and June 30 1971, 215 remained in the program, an overall retention rate of 86 percent.¹⁰ This is close to the rate experienced in similar methadone programs elsewhere in the United States. It should be noted from Table 1

that the CSP program dealt primarily with older addicts (mean age 35.4 years) with long addiction histories and prison records (means: 13.9 years addiction and 4.5 years incarceration).

Table 2 presents descriptive data available on those 34 patients who were admitted to the program during its two years of operation but who were not actively enrolled on June 30 1971. Comparison of Table 2 with Table 1 shows no major statistically discernible differences among these patient groups.

Table 3 shows the sexual and racial composition of patients in the methadone maintenance program. The number and percentages of patients engaged in socially productive behavior on June 30 1971 are recorded in Table 4. It is to be understood that many of these patients were enrolled in the program only a short time and had not had adequate opportunity to reach socially productive levels. We have found that the rehabilitative process for most addicts may take as long as six months to a year. Almost all addicts who had been in our program more than one year were engaged in socially acceptable behavior. During the last six months of the period here reported upon, only four substance-related arrests occurred among this large group of addicts.

The pattern of narcotic abuse by patients varied with the length of time they were in the program. While 27.4 percent of patients show one or more positive reactions to urine tests for narcotics during their ninth week on methadone maintenance, this proportion dropped to less than 5 percent in the 45th week and was zero

during the 90th week of maintenance treatment. These rather striking statistics accurately reflect our clinical observations that few, if any, instances of abuse are seen among the long-term methadone patients. Clearly, they have so decidedly changed their life styles and mental attitudes that illicit use of drugs is no longer a part of their behavior.

Side Effects of Methadone Maintenance

A high incidence of sweating, constipation and weight gain are the major side effects noted in patients receiving methadone maintenance treatment. Other side effects include decreased sexual desire and potency, dry mouth and persistent thirst, drowsiness, loss of appetite, nasal catarrh and nervousness. These secondary side effects occurred in less than 2 percent of patients.

As methadone programs and the numbers of participating addicts expand, the danger of accidental poisoning increases. It must be borne in mind by all physicians that doses normally prescribed for addicts in methadone maintenance programs can be lethal for non-addicted adults and children. Because the pharmacological effects of methadone last more than 24 hours, any physician treating an accidental overdose must prescribe narcotic antagonists to continue for at least 24 hours. Since the duration of effect of most antagonists is short, repeated administration is mandatory.

Methadone Controls

Methadone has been approved by the Food and Drug Administration as an analgesic and an anti-tussive and also for the withdrawal of nar-

TABLE 2.—Statistics on the 34 Patients Who Discontinued CSP Methadone Maintenance Program July 9, 1969-June 30, 1971

	Range	Median	Mean
Age (years)	22-65	34	35.7
Education (years)	3-16	11	11.0
Heroin Addiction (years)	4-29	12	14.2
Duration of Maintenance (weeks)	1-54	8	16.9
Time in Prison (years)	0.1-15	2	3.3

TABLE 4.—Social Adjustment of 215 Patients in CSP Methadone Maintenance Program June 30, 1971

Social Adjustment	Number	Percent
Employed and Socially Acceptable* ...	140	65.1
Unemployed but Socially Acceptable ..	43	20.0
Socially Unacceptable	32	14.9

*Includes patients enrolled in school, training programs and full-time homemaking.

TABLE 3.—Sexual and Racial Composition of 249 Patients on CSP Methadone Maintenance

	Male	Female	Caucasian	Black	Latino	Oriental	Other
All patients admitted							
July 9, 1969-June 30, 1971	73.5%	26.5%	57.4%	28.0%	9.6%	2.5%	2.5%

cotic addicts from illicit substances. However, it is still considered a research drug in maintenance programs even though it has been used for more than nine years and by tens of thousands of narcotic addicts. No major deleterious side effects have been noted during that period.

Private physicians without extensive ancillary treatment back-up are prohibited from dispensing methadone for narcotic addiction. California law clearly prohibits any but specifically authorized physicians from dispensing methadone to known narcotic addicts. Only a physician possessing an Investigational New Drug Permit and permission from the California Research Advisory Panel may prescribe methadone in maintenance doses for addicts.

Conclusion

Traditional treatment methods for narcotic addiction have been dismal failures. The demand that addicts remain abstinent limits the acceptability of this treatment to less than 10 percent. Incarceration has no place in the treatment of the addict. It is inhumane and medically unjustifiable. Other available treatment approaches have met only limited success and appeal to only a few narcotic addicts.

Methadone maintenance, although a relatively new means of treatment, has been remarkably successful in rehabilitating addicts. The San Francisco program achieved an 86 percent rehabilitation rate in a criminal addict population. Although methadone maintenance procedures require the daily administration of an addicting drug, this prophylactic treatment is comparable

to that of insulin for diabetic patients and digitalis for those with heart disease. The major thrust and emphasis of narcotic addict treatment must rest within the medical community. Efforts by legislative bodies to diminish the physician's prerogative to treat addicts must be resisted. The law enforcement complex has had sole domain of narcotic treatment programs for the past 50 years, and we have more addicts today than ever before in the history of our country.

Medical research must continue in an effort to cure narcotic addiction. Encouraging results with narcotic antagonists, including cyclazoline and naloxone, must be investigated further. Since narcotic addiction is a medical pharmacological problem, the treatment answer will be found only within a medical system.

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COLD AID FOR BURNS

Should you apply cold sponges immediately after a burn injury?

There is abundant evidence both in the laboratory and from years of clinical experience that the best thing you can do immediately after a burn (not 6 or 7 hours later) to give that patient comfort is to put on bath towels or some heavy cloth soaked in ice water. If you'll keep that cold for a period of time you will not only take away the pain but you'll actually stop (if you get it early enough) much of the burning insult.

The immediate treatment for all burns is cold.

—CURTIS P. ARTZ, M.D., Charleston, S.C.
Extracted from *Audio-Digest Surgery*, Vol. 18, No. 4, in the Audio-Digest Foundation's subscription series of tape-recorded programs. For subscription information: 1930 Wilshire Blvd., Suite 700, Los Angeles, Ca. 90057

Important Advances in Clinical Medicine

Epitomes of Progress -- Preventive Medicine and Public Health

The Scientific Board of the California Medical Association presents the following inventory of items of progress in Preventive Medicine and Public Health. Each item, in the judgment of a panel of knowledgeable physicians, has recently become reasonably firmly established, both as to scientific fact and important clinical significance. The items are presented in simple epitome and an authoritative reference, both to the item itself and to the subject as a whole is generally given for those who may be unfamiliar with a particular item. The purpose is to assist the busy practitioner, student, research worker or scholar to stay abreast of these items of progress in Preventive Medicine and Public Health which have recently achieved a substantial degree of authoritative acceptance, whether in his own field of special interest or another.

The items of progress listed below were selected by the Advisory Panel to the Section on Preventive Medicine and Public Health of the California Medical Association and the summaries were prepared under its direction.

Reprint requests to: Division of Scientific and Educational Activities, 693 Sutter Street, San Francisco, Ca. 94102

Rabies

Treatment of rabies begins with emergency care of the bite. If the skin is not broken, no treatment is indicated. The wound should be irrigated thoroughly with 20 percent soap solution or some other antiseptic. It must be verified that the biting animal is rabid, if possible. Of all identified rabid animals, approximately 75 percent are wild animals. Records of the Cali-

fornia State Department of Public Health, over an 18-year period and 25,000 examinations, show that gophers, mice, hamsters, squirrels, and similar animals have not had one case of rabies. Biting animals which can spread rabies should be confined for 10 days to see if they show symptoms of the disease. Carriers of rabies, such as bats, should have their brain tissue examined immediately.

Persons with severe bites, especially on the head, should be given antirabies serum and vaccine unless the biting animal has a current rabies vaccination. Serum should be given in a single dose—40 International Units (IU) per kilogram of body weight. At the same time, DEV or Semple vaccine should be started. Daily injections should be continued for 14 to 21 days if the animal is proved to be rabid. Reactions to DEV

vaccine are less likely to occur unless the recipient is allergic to feathers or eggs. Semple vaccine is more likely to cause adverse reactions. If it does, preventive treatment should immediately be changed to DEV. One or two human deaths a year continue to occur in the United States due to lack of preventive treatment, but deaths can occur due to reaction to antirabies vaccine. It is imperative that a careful investigation as to the condition and history of the biting animal can be made before treatment is begun.

Local health departments should be consulted concerning animal bite problems. All animal bites are reportable to it or the agency which confines animals for observation. Animal brain tissue can be examined for rabies in the local public health laboratory or California State Department of Public Health, Virus Laboratory. If antirabies serum or vaccine is needed, the local health department can assist in getting it. Consultation in any diagnostic or treatment problem is also available.

DWIGHT M. BISSELL, M.D., M.S.P.H.

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Methyl Mercury

The existence of environmental mercury contamination became evident only after the recent discovery of "Minimata disease" in Japan. One

hundred and sixty-eight cases of severe neurological disease occurred, with 52 deaths and 23 congenitally brain-damaged infants, were reported in some 400 live births. The elusive cause was finally determined to be the consumption of fish and shellfish contaminated with mercury discharged from chemical plants. Industrial mercury discharges, previously thought to be inert, are methylated by microbial systems in the bottom sediment of fresh and salt water. The methyl mercury thus formed enters the aquatic food chain and undergoes tremendous concentration as it ascends this pathway from smaller to larger species.

The mercury in fish is virtually all in the form of alkyl (methyl) mercury which is many times more toxic than metallic, inorganic or aryl forms of mercury. Inorganic and alkyl mercury poisoning are manifested as two distinct symptom complexes, although some overlapping may exist in heavily exposed cases. They appear to be separate clinical entities showing marked differences in absorption, excretion, specific tissue localization, transplacental migration, pathological picture, occurrence of chromosome damage and reversibility of symptoms.

A second source of alkyl mercury contamination is the use of agricultural fungicides applied to seed grain. This practice has been responsible for several tragic epidemics (Iraq, Pakistan and Guatemala) and the celebrated case of the Huckelby family in New Mexico. It has also caused serious contamination of seed-eating birds, including pheasant in California. In addition, methyl mercury undergoes translocation into the grain grown from the treated seed, thus contributing to wide-spread, if low-level, human and animal exposure to this cumulative toxin. In 1970 almost all seed grain planted in California was treated with alkyl mercury. By the end of 1972, this practice is scheduled to be eliminated.

The FDA "guideline" level of 0.5 ppm for mercury in fish has been critically examined in many quarters and appears to be on a sound basis, although the margin of safety is not large. Pregnant women carry an increased risk, and there is evidence that some persons may be hyper-susceptible to mercury. However, in this country there has been only one reported case of illness attributed to eating mercury-contaminated fish. On the basis of present knowledge it would be unfortunate if public over-reaction

deprived people of the excellent and inexpensive source of dietary protein provided by fish, since almost all commercial fish (other than tuna and swordfish) contain levels of mercury far below the FDA guideline.

EPHRAIM KAHN, M.D.

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Isolation Techniques for Use in Hospitals

Physicians and hospital staff are continuously faced with the need for making decisions regarding proper isolation techniques for patients suffering from a wide variety of illnesses. The Public Health Service has recently published an up-to-date, brief, practical, comprehensive booklet which is an important resource in this regard, for any hospital. The publication noted below is available from the U.S. Government Printing Office in Washington. The current cost is \$1.00 per copy.

DONALD G. RAMRAS, M.D., M.P.H., F.A.C.P.M.

REFERENCE

Isolation Techniques for Use in Hospitals, U.S. Department of Health, Education, and Welfare, Public Health Service, 1970. Public Health Service Publication No. 2054.

Chemoprophylaxis for Malaria

Malaria remains a highly prevalent and serious endemic disease in many tropical and subtropical countries. In recent years, several Californians have acquired malaria while traveling

abroad because they did not receive adequate chemoprophylaxis. Two deaths due to falciparum malaria have been recorded in 1971. Endemic areas where prophylaxis may be needed include Africa, Haiti, Central America, the southern west coast region and southern states of Mexico, South America (with the exception of Venezuela, Uruguay, Chile and Argentina), the Southern Middle East, Southeast Asia, Korea and some islands of the Southwest Pacific region.

It should be recognized that the risk of malaria is not necessarily uniform throughout an entire country and that local conditions to a large extent dictate the need for medication. Each traveler's itinerary should be reviewed to determine whether it will take him into areas in which preventive measures are indicated. With the exception of tropical Africa where the risk of life-threatening falciparum malaria is uniformly high, malaria prophylaxis usually is not indicated when the itinerary includes only major cities usually frequented by tourists.

Chloroquine phosphate (Aralen®) is recommended for chemoprophylaxis of malaria. The adult dosage is 500 mg (300 mg base) once a week starting the week before possible exposure. Suppression should be continued at this dosage throughout the time spent in malarious areas and for at least six weeks thereafter. This regime will provide protection against falciparum malaria with the exception of some strains in Southeast Asia and South America which are chloroquine-resistant.

Infections caused by *P. vivax*, *P. malariae* and *P. ovale* (relapsing species) are not prevented but their symptoms are suppressed. Chloroquine supplies have been temporarily short, but the manufacturer has recently indicated that the drug is again readily available for the treatment and prophylaxis of malaria.

Primaquine phosphate is the drug used for radical cure of relapsing species of malaria. The adult dosage is 26.3 mg (15 mg base) daily for 14 days following return from the malarious area. The routine use of primaquine for all civilians who have been in a malaria endemic area is questionable. Intensity of exposure to relapsing species should determine its use. Primaquine may cause hemolysis in persons with glucose-

six-phosphate dehydrogenase deficiency. For alternate malaria suppressive drugs and schedules and pediatric dosage, physicians are referred to two recent manuals on infectious diseases.

JAMES CHIN, M.D.

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Tetanus Prevention

The most readily prevented of diseases still takes its toll in the United States, even in California. Three hundred fifty-two cases of tetanus were reported in 1968-69 to the National Center for Disease Control; 30 were in California; the case fatality rate remains at about 60 percent, nearly the same as in 1950. In part, this continuing high fatality rate is caused by the increasing preponderance of older people (presumably unimmunized) among the infected. Tetanus occurred five times as frequently among persons past age fifty as among younger people, and these older patients have less probability of survival.

Several recent reports have added to our assurance of the adequacy of the immunity established by three aluminum-adsorbed toxoid injections with an interval of more than four weeks between the first and second and of more than a year between the second and third. A protective level of over 0.01 unit of antitoxin per ml of blood will be maintained for at least ten years, and a single additional injection will promptly boost the antibody level for a prolonged period.

Evidence has been presented that excessively frequent recall injections may cause hypersensitivity to the toxoid. Additional documentation of the needlessness of frequent recall injections has recently appeared, and has evoked editorial comment in favor of sparing use of emergency boosters.

Several observers have proposed that, after a basic immunization, it is sufficient to administer recall injections every ten years. This would continuously maintain a protective antibody level which would obviate the necessity for emergency boosters.

Such a plan would require an accurate, reliable immunization record for each individual, readily accessible for the guidance of physicians in emergencies. Lacking such information, the physician must treat each person with a tetanus-prone wound as if he had not been immunized. A dose of 250 units of tetanus immune globulin (TIG) (human) will immediately provide a protective level of antitoxin in most patients; unusually large persons need more. A larger dose of TIG may interfere with the effectiveness of toxoid given simultaneously. Active immunization with aluminum adsorbed toxoid can be started immediately. (The injection should be in a site different from the TIG.) (This will afford continuing protection after the passive immunization has deteriorated.

Every physician should assure himself that every patient has basic tetanus immunization and renewal every ten years. Special attention should be given to older patients. When the physician has reliable knowledge of continuous protection, he can stop emergency boosters except for those patients with wounds such as those of a farmer ground up by a disc plow in a manured field. The Public Health Service Advisory Committee on Immunization Practices now recommends a recall injection of toxoid, if five years have elapsed since the last dose, for all but minor, clean wounds. For such minor wounds, a recall injection is not recommended before ten years. This is a significant change from the 1969 recommendation.

Diphtheria immunization should generally be given concurrently with tetanus immunization.

RODNEY R. BEARD, M.D.

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Australia Antigen and Viral Hepatitis

The discovery of Australia antigen in the 1960's has provided a valuable marker for epidemiologic studies of viral hepatitis. Initial reports linked Australia antigen with both "infectious" and "serum" hepatitis, however these studies were based on sporadic hospitalized cases of hepatitis in whom the sources of infection often were poorly defined. Subsequent experimental studies have firmly established the specific association of Australian antigen with serum hepatitis. In addition, there have been numerous reports from throughout the world documenting the failure to detect Australia antigen in common-source outbreaks that were clinically and epidemiologically typical of infectious hepatitis.

Until recently, the prevailing view has been that serum hepatitis was transmitted exclusively via the parenteral route and was not a contagious disease. This concept has been modified as studies have shown that Australia antigen-associated serum hepatitis can be transmitted orally as well as parenterally and can spread to contacts, although rather less regularly than infectious hepatitis. These studies confirm isolated epidemiologic observations which suggested that serum hepatitis could be transmitted by close contact as well as by parenteral exposure. Australia antigen has been demonstrated in urine as well as serum. Though postulated, the presence of antigen in feces has not been demonstrated unequivocally at the present time. The observations that both forms of viral hepatitis can be transmitted by the oral and parenteral routes have added force to the non-committal terms type A and type B hepatitis to describe "infectious" short-incubation and "serum" long-incubation forms of the disease, respectively. Type B hepatitis is transmitted more readily by exposure to blood or blood products, because, as indicated by the presence of Australia antigen, the virus

may persist for a long time in some patients, particularly those with anicteric disease who become "healthy" carriers.

The demonstration that type B hepatitis can be spread by contact exposure raises an interesting question regarding the marked increase of viral hepatitis in California during the last several years. The increased incidence has been associated with a marked change in the age distribution of cases. Up to 1960, peak age-specific incidence occurred in children less than 14 years of age, an age pattern epidemiologically consistent with the predominance of type A hepatitis. Since 1960 the incidence in those less than 14 years has remained essentially unchanged, while the incidence in persons 15 to 29 years of age has skyrocketed to rates five times greater than those in children. About twenty percent of the cases in young adults are reported as associated with illicit parenteral drug use. However, no such association is made in the remaining 80 percent.

Coincident with the increase of viral hepatitis in young adults have been profound changes in lifestyle among segments of this age group. Drug use has become widespread, frequently coupled with crowded living conditions, poor attention to personal hygiene and substandard sanitation. Although a matter of speculation at this time, it may be that a significant proportion of viral hepatitis in young adult Californians is in fact contact-acquired, Australia antigen-associated, type B hepatitis. The true extent of the type B hepatitis "iceberg" in adults should become more evident as Australia antigen testing becomes an integral part of the viral hepatitis diagnostic workup. Physicians are urged to include Australia antigen test results when reporting patients with this disease to the health department.

RONALD R. ROBERTO, M.D.

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The Diagnosis and Management of Hyperlipidemia

Increasing attention is being focused on the diagnosis and treatment of hyperlipidemia since its recognition as one of the principal risk factors in the development of atherosclerosis and its serious sequelae such as myocardial and cerebral infarction. The practicing physician plays a key role in both the identification and the management of hyperlipidemia. Not only is reducing abnormally high serum cholesterol and triglyceride levels presumably of value in preventing atherosclerosis, such reduction can also control other distressing manifestations of familial hyperlipidemia such as xanthomatosis and pancreatitis, which often accompany pronounced forms of this disease.

Fortunately, the identification of hyperlipidemia is not difficult and can be performed by simple and well standardized laboratory procedures. Following at least a 12-hour fast, serum cholesterol and triglyceride levels should be no higher than those listed below for each age group.

Age	Upper Level of Normal	
	Cholesterol (mg/100 ml)	Triglycerides (mg/100 ml)
0-19	230	140
20-29	240	140
30-39	270	150
40-49	310	160
50-59	330	190

If the patient is *not* fasting, glycerides greater than 350 mg per 100 ml should be used as a criterion. However, since serum cholesterol is not influenced acutely by diet, the same criteria can be used as for the fasting patient. Analysis of cord blood drawn at birth may also identify at least homozygous infants with familial hyperlipidemia.

If either elevation of serum cholesterol or triglyceride or both is identified by means of primary laboratory screening, the serum lipo-protein electrophoresis, when used as a secondary screen, can usually distinguish between the five different types of hyperlipidemia except, perhaps, for Type III which may require dietary manipulation and serum ultracentrifugation. The physician should also be alert to exclude hyperlipidemia secondary to such diseases as diabetes melitus, myxedema and the nephrotic syndrome.

Specific identification of the five types of hy-

perlipidemia is important since its management is type-specific. For instance, Type I is largely due to dietary fat intolerance and can be best controlled by reduction of dietary fat to 15 percent or less of total calories. Although Types II, IV and V may also require dietary fat restriction, Types III and IV are more sensitive to changes in carbohydrate intake. For instance, Type III is best managed by a balanced diet where 40 percent of calories are derived from carbohydrates, 40 percent from fat (half of which should be composed of unsaturated fatty acids) and 20 percent from protein. Cholesterol intake should also be restricted by cautioning the patient not to eat either "organ meats" such as liver, or egg yolks.

Drug therapy is also type-specific. Although Type I does not require drugs, clofibrate (Atromid-S)[®] may be useful in all of the other four, and therapeutic agents such as cholestyramine and d-thyroxine also have a role.

Since the management of hyperlipidemia requires the kind of patient cooperation required for the long-term treatment of diabetes, the physician should turn to such authoritative sources as those referred to below before instituting what may be a decided change in the patient's lifestyle. Particular emphasis should be placed on the initial identification and vigorous management of hyperlipidemia in childhood, adolescence and early adult life since it is presumed that sequelae such as atherosclerosis can best be prevented by the early institution of a realistic program of dietary management supplemented, when necessary, by drugs.

JOSEPH STOKES III, M.D.

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Treatment of Mild Hypertension

Hypertension without evident cause (essential hypertension) is recognized as a major precursor of a number of serious diseases including coronary artery disease, cerebrovascular disease, and hypertensive heart disease. Effective methods of lowering blood pressure are now available and treatment of moderate and severe hypertension occurring in all ages is standard practice. However, treatment of mildly elevated blood pressure—that is, 90 to 114 mm of mercury diastolic—is not yet fully accepted as standard practice since the side effects of treatment for long periods in younger persons are frequently considered more troublesome than the underlying condition, and in the elderly these levels are sometimes viewed as physiological. Evidence supporting a more aggressive approach is now available from the Veterans Administration Cooperative Study Group on Antihypertensive Agents.

Three hundred eighty men (42 percent Black) were randomly allocated to equal sized treatment and control groups and observed for varying periods of time up to five years. Twenty-five patients died of hypertensive or atherosclerotic complications, 19 in the control group and 8 in the treated group. Considering all morbid events over five years, the control group had a rate of 55 percent compared with 18 percent for the treated group. The benefits were evident from the second year on. While the elderly benefited most, even those under 50 showed an effect. There was no difference in response between the races.

This rigorous study lays to rest the contention that treatment of mild hypertension in men over 50 (and probably in women too, although they were not studied) is not indicated. It appears that substantial benefits in prevention of vascular complications and premature death can be realized with an aggressive therapeutic approach.

WARREN WINKELSTEIN, JR., M.D.

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Malaria

During the past several years there has been a rather dramatic increase in the incidence of malaria first reported in the United States. The vast majority of these cases have occurred in veterans returning from Vietnam.

Personnel returning from Vietnam are prescribed anti-malarial medication to be taken after their return to the United States but many have shown that this medication frequently is not taken. Likewise even in Vietnam the anti-malarial medication prescribed is not taken.

The increased use of heroin among troops in Vietnam has resulted in some veterans continuing to use heroin after their return to the United States. These veterans share needles with other non-veteran drug users and if the veteran develops malaria there is the possibility that he may transmit it to his co-users.

The first such case was reported from Ft. Bragg, North Carolina, in July 1970. In December 1970 a cluster of five cases was discovered in a small community in Ventura County, California. Subsequently, 43 cases have been discovered in Kern County, and isolated cases in Yuba and Los Angeles counties.

Physicians should be on the alert for malaria as a possible cause of unexplained fever, particularly in young adults. Since anopheles mosquitos are present in California, there is also the possibility of spread of malaria from the addict community to the general population.

Blood banks, which usually reject donors who are recent veterans because of the fear of malaria, should be on the alert for malaria in other young donors who are possible intravenous drug users.

ROBERT J. BOESE, M.D.

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Pregnancy Testing

The availability of legal therapeutic abortions in California in the last few years has brought a corresponding increase in the request for rapid, early and accurate pregnancy testing. Health departments, free clinics and physician's offices are daily performing scores of these tests in an attempt to assist women who may have a problem pregnancy or unwanted pregnancy.

Several papers written recently on the immunologic slide and tube tests for pregnancy point out a few of the conditions that may cause false negative or false positive tests such as proteinuria, hyperthyroidism, many of the psychotropic drugs and apparently, use of heroin. These studies were all conducted by trained laboratory personnel under optimum conditions. However, today these tests are often being done by relatively unskilled people. The literature also reports that many of the currently used pregnancy tests go through unexplained periods of unreliability.

Attention must be drawn to the tremendous psychological impact of these tests, and women must be told that they are not 100 percent accurate. A false negative test may mean postponing seeking a therapeutic abortion until it is too late and a false positive test may mean needless heartache, unnecessary operation, and even the possibility of suicide.

Because of the large number of relatively untrained personnel interpreting these tests, because these tests may go through periods of unreliability and especially because of the enormous psycho-social impact surrounding these tests, strict attention must be paid to obtaining accurate results. Adequate training and supervision of ALL people performing these tests, the use of two immunologic tests together (preferably a tube and slide test) and a confirming pelvic examination whenever possible should be done.

MRS. GEORGIANNA SELSTAD

*Maternal & Adolescent Health Coordinator
Ventura County Health Department*

Syphilis and Gonorrhea Therapy

Syphilis therapy calls for low dosages of antibiotic over a long period, while gonorrhea therapy calls for high dosages for a short time. Long-acting repository penicillin is ideal for syphilis, but contraindicated for gonorrhea.

Syphilis

A total of 4.8 million units benzathine penicillin G, administered as 2.4 million units (1.2 in each buttock) at a seven-day interval, will cure syphilis. Patients allergic to penicillin are given 30 to 40 grams of appropriate oral antibiotics over a 10 to 14 day period (tetracycline derivatives, erythromycin).

Gonorrhea

The physician has several antibiotic choices for therapy of gonorrhea, none of which give universally satisfactory results. By injection, aqueous procaine penicillin, cephaloridine or kanamycin are frequent choices. Orally, ampicillin, demethylchlortetracycline, doxycycline, and tetracycline give good results.

Injection therapy should provide high blood levels for 48 hours in males and 72 to 96 hours in females. Best results with oral therapy are obtained from three to four day regimens for males and four to five days for females. Addition of probenecid improves response to penicillin therapy. Long-acting benzathine penicillin G does not provide satisfactory levels and should not be used.

Failure

Most venereal disease clinicians believe that lack of response to treatment is usually "patient failure," not therapeutic. "Ping-pong" reinfection makes epidemiologic therapy on all sex contacts important, both for community control and for cure of the individual case. With oral therapy, patients may overlook the prescribed times for multiple doses or share their medication with contacts and friends.

Limitations of penicillin include fear of anaphylactic reaction in sensitive patients, "relatively" resistant strains, and failure to cure non-specific urethritis (NSU). Tetracycline and its related products are needed for NSU. Tetracycline is contraindicated in pregnancy and is adversely effected by antacids, including milk and juices. Doxycycline and demethylchlortetracycline appear superior to tetracycline and require less frequent administration. Tetracyclines by injection are not well tolerated by patients because of injection-site pain.

The following products and dosages are currently successful therapy for gonorrhea (uncomplicated male urethritis):

Injection

- Aqueous procaine penicillin, 4.8 million units (divided in each hip) probenecid, 5 grams may be added—one gram ½ hour prior to injection, then one gram q.i.d.
- Cephaloridine, 2 grams
- Kanamycin, 2 grams
- Tetracycline, 250 mg. x 2

Oral

- Ampicillin, 3 grams. Given over 3 days: One gram stat; then ½ gram at 4 and 8 hours; then ½ gram b.i.d. (Females given ½ gram b.i.d. one additional day—total, 4 grams.)
- Demethylchlortetracycline, 2700 mg. Given over 4 days: 600 mg stat, 300 mg at 8 hours, then 300 mg b.i.d. x 3
- Doxycycline, 800 mg. (200 mg stat, 100 mg b.i.d. x 3). (Females given 100 mg b.i.d. for two additional days—total, 1200 mg.)
- Tetracycline, 10 grams (1.5 grams stat; then ½ gram q.i.d. x 4).

W. A. KETTERER, M.D., M.P.H.

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Current Street Language for Various Drugs That Are Abused

The use and abuse of psychoactive drugs is a problem of grave concern to medical and public health officials. Reports of increased use among adolescents has led to the establishment of varied forms of treatment facilities, each employing established as well as oft-times innovative modalities. However, effective intervention treatment and social rehabilitation programs have been few, partly because of difficulty in communication. A major component in the use of psychoactive drugs has been the development of a "drug slang."

It is difficult to make any generalizations about the words used, in that the terms are constantly changing and a listing is never up to date. Communities many times also have their own words for drugs, and these terms do not carry the same meaning in other localities. However, there are some terms that seem to be used widely and frequently:

A's	amphetamine
acid	LSD, d-Lysergic acid diethylamide tartrate
Acapulco gold	high-grade marijuana
angel dust	DMT or PCP sprinkled over parsley or tobacco
bag	packet of drugs
barbs	barbiturates
bennies	Benzedrine® (brand of amphetamine sulfate)
blue angels	} amobarbital sodium
bluebirds	
blue heaven	
blue devils	
blues	
blue velvet	paregoric in combination with amphetamine or antihistamine such as Pyribenzamine® (brand of tripeleonnamine)

buttons	dried tops of the lophophora cactus (peyote)	gee-head	paregoric user
bombido	injectable amphetamine	gold dust	cocaine
businessman's trip	(see DMT)	hash	hashish (resin from cannabis)
booze	alcohol	hyke	Hycodan® (dioxycodinone)
babo	Nalline® hydrochloride (brand of nalorphine)	horse	heroin (diacetyl morphine)
Beast (the)	LSD	H	heroin (diacetyl morphine)
Big "D"	LSD	Harry	heroin (diacetyl morphine)
Blue Cheer	type of LSD	hearts	Dexedrine® (brand of dextroamphetamine sulfate)
bagging	sniffing glue in a bag	hay	marijuana
Bernice	cocaine	J	marijuana cigarette
black	LSD	joint	marijuana cigarette
black beauty	methamphetamine	jug	ampoule of injectable drugs
blues-and-reds	(see Rainbows)	junkie	heroin user
bullets	Seconal® (brand of secobarbital sodium)	junk	heroin (diacetyl morphine)
bombers	large marijuana cigarettes	key	kilogram of marijuana
cap	capsules	lid	one ounce of marijuana (approximate)
coke	cocaine (extract of dried leaves of erythroxylon coca)	llesea	Mexican term for marijuana
cokie	cocaine addict	locoweed	Jimson weed (datura stramonium)
chipping	periodic use of intravenously used drugs	meth	methamphetamine
Charlie	cocaine	Mexican Brown	brown marijuana from Mexico
crystal	methamphetamine hydrochloride (powdered or crystalline form)	mota	Mexican term for good marijuana
candy	barbiturates	M	morphine sulfate
cartwheel	white, round, double-scored amphetamine tablet	mesc	mescaline (resin from lophophora cactus) (peyote)
chalk	methamphetamine hydrochloride (powder form)	magic mushroom	mushroom (psilocybe Mexicana) containing psilocybin
Christmas tree	Tuinal® (brand of amobarbital sodium and secobarbital sodium)	Mickey	combination of alcohol and chloral hydrate
co-pilots	amphetamines	Miss Emma	morphine sulfate
Chicano green	type of dark green marijuana	nembies	pentobarbital sodium
Cristina	methamphetamine hydrochloride	number	marijuana cigarette
crank	methamphetamine hydrochloride	orange sunshine	form of LSD
crap	heroin	Panama red	potent grade of marijuana from Panama
DET	diethyltryptamine	P.G.	paregoric
DMT	dimethyltryptamine	piece of stuff	one ounce of heroin
DOM	dimethoxymethamphetamine (see STP)	pot	marijuana
dollies	Dolphine® (brand of methadone hydrochloride) tablets	powder	amphetamine sulfate in powder form
downers	non-narcotic central nervous system depressants	purple hearts	Dexamyl® (brand of dextroamphetamine sulfate and amobarbital sodium)
dexies	Dexedrine® (brand of dextroamphetamine sulfate)	peace pill (P.C.P.)	Sernylan® (brand of phencyclidine) an anesthetic originally for dogs
dynamite	high-grade heroin	peanuts	barbiturates
dust	cocaine	pinks	secobarbital sodium
flake	cocaine	popper	amyl nitrate in ampule form (generally sniffed)
footballs	amphetamine tablets (oval-shaped)	R.D.'s	secobarbital sodium
gage	marijuana (term seldom used)	red devils	secobarbital sodium
geeze	injecting heroin	reds	secobarbital sodium
goof balls	barbiturates	roach	butt of marijuana cigarette
grass	marijuana (dried leaves, seeds and stems of cannabis sativa)	rainbows	Tuinal® (brand of amobarbital sodium and secobarbital sodium) (red and blue capsule)
		reds and blues	see rainbows
		smack	heroin (diacetyl morphine)
		shit	heroin or marijuana

Simple Simon psilocibin (psilocybe Mexicana) from
the Mexican mushroom

snow cocaine

speed methamphetamine

splash methamphetamine

stuff heroin (diacetyl morphine)

STP dimethoxymethamphetamine
(see DOM) (serenity-tranquility-peace)

scat heroin (diacetyl morphine)

scag heroin (diacetyl morphine)

school boy codeine

uppers C.N.S. stimulants (xanthine alkaloids,
seldom) (amphetamines, often)

weed marijuana

window panes LSD in gelatin sheets

yellow
jackets
yellows

pentobarbital sodium

pentobarbital sodium

G. A. HEIDBREDER, M.D., M.P.H.
BRUCE WOOLLEY

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Los Angeles

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Berkeley

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School of Medicine

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and Public Health, Secretary
Santa Cruz

LAURI THRUPP, M.D.
University of California, Irvine
College of Medicine

Cost Accounting Health Care

THE OVERALL BILL FOR HEALTH care appears to be increasing at the alarming rate of some five or ten billion dollars each year. So far there seems to be little prospect of any real reversal of this trend. A state of national crisis has been declared, but no one seems to have any very clear idea about what to do. There has been a great deal of excited rhetoric, much of it accusing physicians of being the cause of it all. Emergency measures of various kinds have been invoked, many of them discriminatory against physicians or others, or else illogically at cross purposes with the goals being sought in health care. The crisis solutions which have been tried have so far done little except to compound the problems they sought to solve and to produce confusion and dissatisfaction. Meanwhile the health care bill has kept getting larger.

It would appear that an initial step toward a more rational approach would be a more accurate and quantitative assessment or cost accounting of health care. By this is meant that those things which contribute to the ever rising health care bill should be identified for what they are and their part of the total cost quantitated. So far there has been very little effort to do this.

Some of the more obvious causes of rising costs are easily cited. Inflation alone adds several billions of dollars to the total health care bill each year. But there are other causes which are probably even more important. For instance, more sophisticated medical services which are a result of scientific and technologic advances are very likely to cost more. The kind of sophisticated care that can be given in a modern coronary care unit obviously costs more than the simple bed rest and oxygen tent of yesteryear.

But the extent to which the recent widespread development and use of coronary care units has added to the total health care bill has not really been measured. Or in another vein, the decision to eliminate degrading charity for patients and to bring underpaid health care workers up to parity with the rest of the labor force in terms of pay, fringe benefits and working conditions is certainly adding substantially to the health care bill, and further unionization of health professionals will increase it even more. The extent to which all this has increased and will increase health care costs has not yet really been measured. In passing, it may be noted that the take-home pay of the average physician is now probably little if any greater than what many a trade unionist would earn were he to work at his trade the same number of hours and days and nights a week as do most practicing physicians. Or again, the government decision to try to make health care services of high quality equally available to all was and is bound to raise the national health care bill roughly in proportion to the extent this effort to deliver more services to more people succeeds. These examples suggest that progress in medical science, progress on the labor front in health care and success in delivering more services to more people are among the major reasons why the overall health care bill is rising. Any significant reduction of costs in any of these areas is unlikely.

But there are many other components of the overall health care bill. More attention to some of these areas might result in some significant reductions in overall costs. If this is to be done it is essential that these components be recognized as an important segment of the total health care bill and that they be cost-accounted with respect to their part of the bill.

This special issue on Traffic Medicine serves to draw attention to one of a variety of such components. Elsewhere it is pointed out that the casualties, dead and injured, which occur annually due to traffic injuries on the streets and highways of this nation far exceed the total American

casualties, dead and injured, of the entire Vietnam War to date. Traffic injuries, then, must be a very expensive component of the health care bill. There are many other examples of what might be called socially engendered causes of rising health care costs which should be taken into account. For example, changing social attitudes have greatly increased the number of vasectomies, hysterectomies and legal abortions which now appear on the health care bill. For another example, changing sexual mores have given rise to a rampant and as yet uncontrolled epidemic of venereal diseases whose victims require health care services. Ours is a nation of drug and medicine users, even of drug dependents, both in the straight culture and in the counter-culture, and this, aided and abetted by advertisers and the news media, contributes significantly. Very little is known about the effects of pollution, poverty, poor nutrition or cultural and educational deprivation on health care costs. The impact of overuse of alcohol is more obvious. It is irrational to hold physicians, health professionals or even the health care industry responsible for these socially engendered causes of rising health care costs or to expect them to contain them.

By tradition the health care bill also has included many custodial services which are really not health care at all. These either should not be cost-accounted to health care or else they should be clearly identified for what they are. Costly cost controls, the ever growing administrative demands by government, third party payors and others, and the necessity imposed by society for health professionals and health facilities to practice more and more defensive medicine are all increasing daily and all are adding significantly to the causes of rising health care costs. Conceivably some or many of these kinds of growing costs could be reduced through more enlightened policies and procedures on the part of government and others.

If the causes of rising health care costs are somewhat as have been outlined, as seems likely, then better cost accounting of the various components of the health care bill would seem to be an essential step which should be taken soon if any real progress in reducing these costs is to be made. Excited rhetoric, emergency measures and crisis solutions have so far accomplished very little and obviously will never suffice. Some

components of the overall health care bill can probably never be reduced, and in fact they will have to be increased if the national goals are ever to be achieved. But an objective cost accounting of health care could do much to indicate where the costs are actually coming from and where it is likely they can be reduced. For example, certain services which are traditional and widely used may not be worth the cost. This might be the case with some widely used screening procedures. Or the overall need for services might be reduced. This might be the case if more emphasis on "traffic medicine" were substantially to reduce the number and severity of traffic injuries and consequently the amount of health care rendered.

It can only be concluded that cost accounting of health care is something which is very much needed and that serious attempts should be made to do this reasonably, objectively, and soon.

—MSMW

Methadone Treatment Of Opiate Addiction

POINTING TO THE HIGH rates of rehabilitation of heroin addicts in methadone maintenance programs, Dr. Ramer in the current Medical Staff Conference printed elsewhere in these pages urges that opiate addiction be dealt with as a medical problem, rather than by criminal sanctions. It is one of the ironies of medical history that the recent success of methadone maintenance in treatment of opiate addiction required the criminal approach to addiction which preceded it. The idea of opiate maintenance for addicts is an old one. Perhaps with the awareness that some of the giants of medical history were addicted to opiates during their most productive years, many physicians have long suspected that with a regular supply of opiates of controlled dosage and composition, addicts might function in a socially normal manner. Certainly until the Harrison Act became law many physi-

cians attempted to treat addicts this way and the British approach to treatment of opiate addiction is based on this premise.

Previous attempts at opiate maintenance have failed or been flawed, as in the British case, by the difficulties in clinical practice of controlling abuse of prescribed opiates. There is no magic in methadone itself; pharmacologically it differs from other opiates in only minor, if useful, ways. The unique success of the methadone maintenance programs in the last ten years has been due to the fact that since prescriptions of opiates for the treatment of addicts was illegal, the programs were initiated under the rigid canons of clinical research on a "new" drug. The elaborate set of controls characteristic of sophisticated clinical research were the real reasons for clinical success.

As a research program we do not really need endlessly to replicate the 80 to 90 percent maintenance and rehabilitation rates now reported from a number of our centers. Yet, for both social and humanitarian reasons, we in medicine should attempt to extend this success rate to the treatment of the entire opiate dependent population of the United States. In doing this, we must not forget our mistakes of the past. This expansion must be done by organizations capable of scrupulous surveillance of both personnel and large groups of patients. Criteria of selection of patients must be coordinated to prevent shopping. The effort has to be organized to prevent addicts from entering multiple programs and to

prevent methadone supplies from appearing as a street drug. On a small scale these problems have appeared already. We are clearly describing a public health effort rather than an addition to the treatment repertoire of the solo physician.

The rigorous conditions necessary for the relative success of methadone maintenance programs immediately expose the gaps in our knowledge of opiate addiction from biochemistry to human motivation. Yet the success of methadone maintenance adds some intriguing leads. Many addicts report desiring the "flash" when they inject heroin, but they are willing to do without this in a methadone maintenance program. Street addicts seek higher and higher doses of heroin as they become tolerant of the drug, but they are willing to do without this on a methadone program. Neither the threat of punishment nor enforced abstinence has shown any effect in reducing opiate usage; yet addicts are as averse to crime and jail as anyone else, which is why they seek out methadone programs.

These new observations, along with many older ones, are pieces of a puzzle that remain to be put together. Methadone maintenance is the best we have for the chronic opiate addict now. We will have to put the puzzle together to get the real answer.

J. BARRY DECKER, M.D.

*Acting Program Chief
Community Mental Health Services
San Francisco Department of Public Health;
Assistant Clinical Professor
Department of Psychiatry
School of Medicine
University of California, San Francisco*

CYSTS AND SOLIDS BEFORE THE MENOPAUSE

In a premenopausal woman, how long may one continue to aspirate recurrent cysts?

Indefinitely, I would say. We do not aspirate cysts that are fluctuant. If you have a firm cyst and you cannot decide whether it's a cystic or a solid lesion, you should aspirate it to make the diagnosis. If it's a solid lesion, it should be operated upon promptly just as in the case of any other solid lesion suspected of being carcinoma. If it's a cyst it should only be operated upon if it reappears within the next several weeks. We follow them for two, three, and sometimes four weeks. If a firm lesion appears in that period or if the cyst aspirant is bloody, we feel that excisional surgery for biopsy purposes is essential. So we continue to do this indefinitely as long as the cysts appear and we can't differentiate them from solid lesions.

—GEORGE P. ROSEMOND, M.D., Philadelphia
Extracted from *Audio-Digest Surgery*, Vol. 18, No. 1, in the Audio-Digest Foundation's subscription series of tape-recorded programs. For subscription information: 1930 Wilshire Blvd., Suite 700, Los Angeles, Ca. 90057

Special Article

The Destruction of a Medical Center By Earthquake

Initial Effects on Patients and Staff

RONALD R. KOEGLER, M.D., AND SHELBY M. HICKS, M.D., *Sylmar*

"DEDICATION HELD SATURDAY FOR OLIVE VIEW MEDICAL CENTER"

"Elliott L. Richardson, U.S. Secretary of Health, Education and Welfare joined local dignitaries at ceremonies January 9, 1971, in Sylmar that marked the formal dedication of the \$28.5 million Olive View Medical Center. An estimated 400 persons attended the dedication. Supervisor Warren M. Dorn termed the six story, 888 bed hospital as the County's largest and best equipped specialized general hospital."

—News report, January 10, 1971.

"QUAKE!"

"A killer quake that struck the Los Angeles metropolitan area at 6:01 A.M. today apparently hit hardest in the North San Fernando Valley area where loss of life and property damage is staggering. Hospitals, especially Olive View and San Fernando V. A. are scenes of death and destruction. Supervisor Warren Dorn visited Olive View and described the new medical center as 'a total wreck'."

—News report, February 9, 1971.

ON FEBRUARY 9, 1971, an earthquake literally destroyed the Los Angeles County-Olive View Medical Center. The main hospital, a new six story, \$26 million complex, had been dedicated on January 9, 1971; a few minutes after 6:00 A.M. on February 9 it was a twisted ruin (see Figure 1).

We needed only "after" pictures to show the effects on the main hospital building. There was considerable damage at some points (Figure 1),

From Los Angeles County-Olive View Medical Center, Sylmar.
Submitted September 29, 1971.

Reprint requests to: R. R. Koegler, M.D., Community Mental Health Center, Los Angeles County-Olive View Medical Center, 14445 Olive View Drive, Sylmar, Ca. 91342.

but the basic structure was intact (Figure 2). However, the Community Mental Health Center building looked quite different after the quake. In a news picture after the event the building appeared to be a one-story structure not badly awry, with only overturned concrete benches and a scattering of debris as aftermath of the severe shake (Figure 3). But the same building was shown in a picture taken before the quake (Figure 4) to have not one story but two. Few pictures of the Mental Health building appeared in the news media after the earthquake for the hurrying reporters did not realize that the lower story had been crushed flat beneath the upper. Since the majority of the staff had offices in the crushed first floor, their awe when they arrived for work at 8:00 A.M. can be appreciated.

There have been vivid newspaper, magazine, radio and television accounts of what happened. We thought that an additional report, one featuring staff and patient reactions, would be valuable and of interest to the medical community for several reasons. First, the media accounts varied from being incomplete to being grossly inaccurate in their description of the actual events. Second, reports by lay persons, even when accurate, were not sensitive to the type of observations which would be of value to physicians. Finally, persons familiar with the Medi-



Figure 1.—An example of the destruction caused at the main hospital building of Olive View Medical Center by earthquake February 9, 1971.



Figure 2.—Overall view of the main hospital building at Olive View Medical Center after the earthquake.

cal Center (physicians in particular) were in a better position to evaluate the physical and psychological effects on the Center.

In this first report there is emphasis on mental health patients because we were more familiar with these patients and could better evaluate changes in their behavior.

Immediate Effects

At the time of the quake, 6:01 A.M., all patients were either on the second floor of the two-story Community Mental Health Center or on the third through sixth floors of the six-story main hospital building.

Main Hospital

There were 554 patients in this recently dedicated structure: 225 adults with tuberculosis and other chest diseases; 27 pediatric patients with tuberculosis; 116 general medical; 9 non-tubercular pediatric; 44 rehabilitation; 37 surgical; and 96 mental health patients.



Figure 3.—The "one-story" Community Mental Health Center at Olive View Medical Center after the earthquake.



Figure 4.—The two-story Community Mental Health Center at Olive View Medical Center before the earthquake.

One of the medical nurses on duty described the experience vividly: "There was a roar which grew louder and louder. The building was shaking and swaying. I couldn't stand up. The next thing I knew I was on the floor—there was plaster dust everywhere. No one panicked and I didn't see any hysterical behavior. These were all general medical patients and they came out of their rooms after the initial shock and appeared to be waiting for some orders or directions from the staff. My immediate thought was to get the patients out of the building and at the same time I was worried about whether somebody had been injured.

"The elevators were not working—there was no electrical power. I remember how dark and unreal everything was as we led the patients down the stairwell—it was twisted and broken. I remember being frightened."

One hospital aide said: "I felt as if time had come to a standstill. It seemed as if we were the only ones alive in the whole world. No one seemed to be very frightened at first. Everyone

immediately began to evacuate the patients. Later on, as the aftershocks began, there was more evidence of fear. The patients were very cooperative and helpful."

The main hospital building remained twisted but standing, except for the exterior stairwell (fire escape) towers which broke away from the main structure. Three of these six-story wings toppled over, one carrying a heroin addict to the ground, dazed but unhurt inside the building after his six-story fall. He was still drug-free five months later, so we may have discovered a new (albeit expensive) way to treat drug addiction.

Community Mental Health Center

The second floor of the Community Mental Health Center's two-story structure was occupied by 55 patients on two wards. The quake caused the second floor to sink, fairly intact, crushing the first floor outpatient clinic and day hospital to a pile of compressed rubble. Fortunately, at 6:01 A.M. the first floor was unoccupied. It was interesting that most of those on the second floor had little or no sensation of sinking even though the floor settled about eight feet in a few minutes. A member of the staff on duty there said: "At the time of the shock, I was thrown violently across the room against another staff member. We were unable to stand. Dust seemed to come boiling up from everywhere. The noise was frightening. I had a feeling of urgency and wondered if I had time to do whatever was necessary to get the patients out. The entire staff almost immediately began to assemble the patients in small groups, having them hold hands. We only had trouble with two of the male patients who did not want to hold the hand of another male patient." (All three had previously been felt by the staff to be struggling with homosexual urges.) "We could not get the front door open and the patients were led to a back stairway, where we found that the stairway was crumpled and we saw that we were at ground level and no longer needed a stairway. We had not felt the building settling and this was our first realization that our second floor had descended about eight feet and the first floor seemed to have disappeared."

Another aide said that the roar was extremely loud, that the acoustical tiles fell from the ceiling, and that the dust and darkness were frightening. She said that patients rushed to the

nursing station and all those she saw were cooperative and had not panicked.

"I woke up as I was falling out of bed onto the floor," said one 27-year-old paranoid schizophrenic. "Wow, man, the whole world was falling apart. All I wanted to do was get back into bed, but the bed was sliding across the floor. I managed to catch the bed and climb in, but had to lie on my face and grab both sides to keep from falling off. I heard a voice say, 'Everybody get in the doorways.' I remember shouting back, 'Hell, I can't turn loose of the bed!'"

"When the shaking stopped I headed toward the nurse's station and we joined hands and left the building. I don't remember being scared." (He did not place any paranoid interpretation on the quake or personalize it in any way.)

The other patients also held up very well. There is a general belief that psychotic patients become temporarily rational during emergencies. We have some evidence that this is *partly* true for *some* patients. There are interesting observations and comments concerning the patients' reactions. One patient, considered the most mentally disturbed patient on his ward, behaved in a more rational and concerned manner during the quake. He dressed another patient who was almost blind, protected him and led him from the building. Observed shortly after leaving the building, he appeared to be in total contact; however, an hour later he was back in his usual psychotic state.

In another ward there were several patients who had been extremely violent. One patient, especially, was considered the most violent in the hospital. During the tremor he rushed into the room of a young female hebephrenic schizophrenic who had required nasal feedings because she had refused to eat. He took her in his arms and carried her from the building.

In general, a number of acute schizophrenic patients (but not all) did react more rationally during this emergency. Some seemed to revert back to their pathologic state within an hour or two after the crisis. In a few regression took up to two weeks, but none retained any definite noticeable improvement longer than that. Sixty percent (of the actively psychotic) showed no change during or after the quake. Several agitated patients actually became more excited. Patients with severe neuroses tended to react very

rationally, efficiently helping in the evacuation. The patients who did not seem to show any change whatsoever were the severely depressed. They remained severely depressed.

It was interesting to see the behavior of the heroin addicts who were on methadone withdrawal. They tended to continue to demand medication, even immediately after the quake when they knew that the pharmacy supply of methadone was trapped under the rubble. Several addicts had previously broken into and rifled the ward cabinet of methadone and other drugs before leaving the building. Four narcotic addicts used our inability to immediately give them medication as rationalization to disappear into the community, presumably to find heroin.

The Remainder of the Day

Medical, surgical, chest, tuberculosis, and pediatric patients were transferred to Los Angeles County-USC Medical Center, to Rancho Los Amigos Hospital and to other county facilities. Buses, private automobiles, helicopters and ambulances were used, and the transfer went well with minimal discomfort for the patients.

Mental Health patients from both buildings were taken to a grassy plot of ground adjacent to the old unused dining room. As they assembled here, each patient was interviewed by the chief of the admitting emergency service. A decision was made as to whether the patient could go home or be transferred to some other facility. Eighty patients were transferred to Camarillo State Hospital, 24 to UCLA Neuropsychiatric Institute, and ten to self-help narcotic programs, and, as was previously mentioned, four narcotic addicts disappeared into the community. Twenty-three patients were discharged to home care. One of the authors returned to the mental health building and entered the second floor (now the first floor) accompanied by a fire captain. They removed the inpatient record files in order to send them along with the patients to their new hospitals. This allowed medication to be properly continued—extremely important in the case of barbiturate addicts who were undergoing withdrawal therapy. Outpatient records were in the crushed first floor and could not be rescued.

Care of patients was only briefly interrupted and transportation to other hospitals was quickly arranged. During the first day there was little

time for discussion of the earthquake and its destructive effects. Even after the initial shock began to wear off the patients remained calm, perhaps because they were with ward personnel whom they knew. Patients accepted the reassurance of the staff without much questioning. As they boarded buses on their way to other hospitals, many patients smiled and waved to staff members and to other patients, even though they may have suspected that they would never meet again.

"I Did It!"

Two paranoid schizophrenics assumed full responsibility for the disaster. One woman, aged 49, had been admitted against her will; while in the hospital she had been frequently heard shouting loudly, "God will destroy you all." She openly implored God to destroy the building and the staff because they wouldn't release her. The earthquake frightened her and she became hysterical. She cried, begging forgiveness of God for the destruction of the building (which she knew that she had caused). This tearful self-recrimination continued afterward, even several hours later, as she was boarding the bus for another hospital.

The other patient who felt that he had brought on the disaster was a 28-year-old man. For several months he had been saying that he had access to supernatural powers which he was "afraid to use." He fought against accepting these powers from a powerful "person" who was offering them to him. When the quake occurred, he knew that in some way he had accepted the power and through this power had destroyed the medical center. Frightened, he was heard saying over and over, "I didn't mean to do it," as he was led from the wrecked building.

Humor among the Rubble

Despite the tremendous damage, only three persons died at Olive View during the earthquake. Two patients with terminal chest disease died when power failed and their respirators stopped. One ambulance driver was killed when he was struck by falling concrete while attempting to leave the building. All deaths were at the main hospital, none at the Mental Health building.

There was a general feeling of relief as every-

one began to realize that patients and co-workers were still alive. Slowly humor began to reappear. Some of it was of the gallows variety, but there was also a reaction to genuinely humorous incidents occurring during the tragedy.

Two examples come to mind. One incident involved an alcoholic patient who was seen leaving the grounds shortly after being evacuated from the hospital. He walked 14 blocks to a damaged liquor store, took a bottle of wine and returned. It seemed funny at the time, but (in retrospect) he may have been the most realistic person among us. Another humorous incident occurred when the surgical ward was being evacuated. Attendants had a very difficult time getting one patient to leave the hospital.

She had casts on both legs and refused to leave without her bed. Finally, over her protestations, she was placed on a stretcher and carried out through the interior stairwell.

There are, of course, many other incidents which could be mentioned. The point is that the gradual return of the ability to see humor among the tragedies marked the beginning of the ability to plan for solutions to the long-term problems brought on by the destruction of the hospital: What will happen to these patients? What will be the long-term psychological effects? How and when will the hospital be rebuilt? How will the medical needs of the area be served temporarily? How will the staff respond? The answers will come as time passes.

EVALUATING NOISY BREATHING IN INFANTS

In infants with noisy breathing, the phase of respiration in which the noise occurs depends primarily on the location of the obstruction. In lower respiratory tract obstruction where dilatation of the bronchi occurs during inspiration and where contraction of the bronchi occurs during expiration, one tends to hear the sound mainly on expiration. . . .

On the other hand, when the lesion is in the upper respiratory tract, the noise tends to occur primarily on inspiration. The diameter of the airway at the level of the larynx does not alter significantly during inspiration and expiration because of the bony and cartilaginous skeletons of the upper airway, and partial obstruction in this upper part of the respiratory tract tends to produce an inspiratory noise.

Just as the noise varies with the phase of respiration, so the relative length of the two phases of respiration depends primarily on the site of the obstruction. With upper respiratory obstruction one has a prolonged inspiratory phase and a relatively brief expiration whereas with bronchial obstruction one has a prolonged expiration and a brief inspiratory phase.

This is best illustrated by the patient with croup who has a long inspiratory phase and a very brief expiratory phase as opposed to the individual with asthma, who due to the bronchospasm, has a prolonged expiratory phase and a very brief inspiratory phase. Such individuals have very little difficulty getting air in; they have a great deal of difficulty getting air out.

In the presence of lesser degrees of obstruction, one may not hear any noise. The only thing one might observe is the difference in the length of the inspiratory and the expiratory phases.

—JAMES B. SNOW, JR., M.D., Oklahoma City
Extracted from *Audio-Digest Otorhinolaryngology*, Vol. 3, No. 7,
in the Audio-Digest Foundation's subscription series of tape-recorded programs. For subscription information: 1930 Wilshire Blvd., Suite 700, Los Angeles, Ca. 90057

CMERF—How You Can Support It

DURING THE TEN YEARS OF ITS existence, the California Medical Education and Research Foundation, a subsidiary of the California Medical Association, has demonstrated its capability of engaging in educational and research activities on behalf of the public and professional interest.

CMERF, as physicians of California are well aware by this time, is supporting continuing medical education efforts, is providing funds to medical schools for preceptorship programs, is supporting, each year, four-year college scholarships for five merit and two achievement (minority group) high school graduates interested in entering the health sciences fields, is providing support to continuing medical education departments of medical schools, has partially funded two programs in county medical societies relating to accessibility of care and health information, and has completed studies or engaged in other activities concerned with the social and economic problems of medical care and of medical practice.

The California Medical Education and Research Foundation was established in August of 1961 as a nonprofit, tax exempt, California corporation. On October 29, 1963, the U.S. Treasury Department designated the California Medical Education and Research Foundation as a charitable, educational, and scientific organization under Section 501 (C) (3) of the Internal Revenue Code. Contributions are deductible by donors as provided by Section 170 of the Code. The activities of CMERF have demonstrated that not only can it provide a stimulus for the initiation of innovative methods for the organization, delivery and financing of medical care to the people of California, it can also help to assure the continuation of many of the projects in medical education which are in integral part of the activities of the California Medical Education and Research Foundation.

Whereas support of our Foundation has previously come from private and public agencies, including the Audio-Digest Foundation, the board of directors now feels that greater efforts should be expended in providing individual physicians and various community organizations with an opportunity to support its work not only in its on-going activities, but for the future as well.

At the conclusion of this article are some of the forms which may be used in making bequests for medical education and research in the social and economic aspects of medical care and medical practice. Physicians are invited to use whichever form represents the expression of their intentions. They are also asked to call this opportunity to the attention of their friends, acquaintances, patients and organizations which may be interested in contributing to the Foundation dedicated to the improvement of the health of the public.

The cooperation of physicians in the fund-raising endeavor of the California Medical Education and Research Foundation is most sincerely appreciated.

ROBERTA F. FENLON, M.D.

President, California Medical Education and Research Foundation

Suggested Bequest Forms

The following are some of the forms which may be adapted in making bequests for medical education and research in the social and economic aspects of medical care and medical practice. Prospective donors would be well-advised, however, to consult with their lawyers on the exact language to be used, so that the bequest is a true and legally valid expression of their intentions.

1. To convey a cash bequest to the California Medical Education and Research Foundation (CMERF).

(For use when the object is support of research in general.)

"I give and bequeath to the California Medical Educa-

tion and Research Foundation (CMERF), 693 Sutter Street, San Francisco, California 94102, the sum of dollars (\$.....) to be used for medical education and research in the social and economic aspects of medical care and medical practice.”

2. To CMERF for general purposes.

(For use when CMERF will apply and allocate the funds, and when the object is support of medical education in general, and research in the social and economic aspects of medical care and medical practice.)

“I give and bequeath to the California Medical Education and Research Foundation (CMERF), 693 Sutter Street, San Francisco, California 94102, the sum of dollars (\$.....) to be used, at the discretion of its Board of Directors, for medical education and research in the social and economic aspects of medical care and medical practice.”

3. To CMERF for general purposes with expression of intent.

(For use when CMERF will apply and allocate the funds, and when the object is to allow the CMERF to use its discretion in applying the funds in support of medical education and research in the social and economic aspects

of medical care and medical practice, but where the donor wishes to convey his nonbinding desire as to how the funds might be used.)

“I give and bequeath to the California Medical Education and Research Foundation (CMERF), 693 Sutter Street, San Francisco, California 94102, the sum of dollars (\$.....) to be used, at the discretion of its Board of Directors, for (medical education) (research in the social and economic aspects of medical care and medical practice).

“However, this expression of my desire is not to limit the ability or right of the Board of Directors to use the money for any other research which it feels more essential.”

4. To CMERF for categorical purpose.

(For use when the donor wishes CMERF to restrict the use of his funds to a certain category of research and activity.)

“I give and bequeath to the California Medical Education and Research Foundation (CMERF), 693 Sutter Street, San Francisco, California 94102, the sum of dollars (\$.....) to be used for (medical education) (research in the social and economic aspects of medical care and medical practice).

CASE REPORTS

Refer to: Bernard JD, Larson MA, Norris FH Jr: Thyrotoxic periodic paralysis in Californians of Mexican and Filipino ancestry. *Calif Med* 116: 70-74, Feb 1972

Thyrotoxic Periodic Paralysis In Californians of Mexican And Filipino Ancestry

J. D. BERNARD, M.D., M. A. LARSON, M.D.,
Stockton, AND F. H. NORRIS, JR., M.D.,
San Francisco

THE DIFFERENTIAL DIAGNOSIS of acute flaccid paralysis includes the periodic paralyses, although these are usually thought of as rare, familial disorders. A nonfamilial type of hypokalemic periodic paralysis complicating hyperthyroidism, thyrotoxic periodic paralysis (TPP),^{1,2} is common in Japan³⁻⁵ and other areas with large Japanese communities.⁶ TPP also occurs in Chinese^{7,8} and Koreans.^{9,10} Single cases have been described in a Cambodian¹¹ and a Filipino.¹² TPP has been reported in Caucasians^{1,13} but has been seen rarely in the United States except in the West Coast areas with major oriental immigrant populations.

We describe here an unusual experience with TPP in patients having Mexican or Filipino ancestry. In five of six consecutive cases during a five-year period the patients were of this ethnic background (Table 1). Physicians throughout the southwestern United States should be alert to the

possibility of TPP as a cause of episodic weakness in patients having such family origins.

Case Reports

Case 1. A 27-year-old mechanical engineer of Japanese extraction was admitted for evaluation of periodic paralysis. Four years before admission, he noted a five-minute episode of "stiffness" in his thighs, followed by episodes of leg paralysis. The most severe attack was approximately two months before admission when, during the night, he awoke paralyzed following a hunting expedition and a large meal late in the evening. The attacks lasted from five minutes to 12 hours. Direct questioning disclosed heat intolerance and excessive sweating. There was no family history of thyroid or neuromuscular disease.

On physical examination the resting heart rate was 110 beats per minute and blood pressure 150/80 mm of mercury. The skin showed changes typical of hyperthyroidism, but there were no demonstrable eye signs nor was the thyroid gland enlarged.

The laboratory results are presented in Table 2. A serum potassium determination was 3.5 mEq per liter when the patient was asymptomatic.

He was treated initially with propylthiouracil, with good result. Later he discontinued the medication and two years later all the symptoms recurred. He was re-evaluated at another hospital, where subtotal thyroidectomy was performed. He has had no further episodes of paralysis and is clinically euthyroid.

Case 2. A 26-year-old Mexican-American man presented with a six-month history of severe weight loss, heat intolerance, hyperphagia, excessive sweating, and eye prominence. Approximately one month before his first evaluation, he noted the first of six episodes of weakness, most of which progressed rapidly to paralysis of the legs. These attacks usually occurred during the night. There was no family history of thyroid or neuromuscular disease.

From the Medicine, Neurology, and Nuclear Medicine Services of the San Joaquin General Hospital, Stockton, and the Institute of Medical Sciences, Pacific Medical Center, San Francisco.

Submitted April 15, 1971.

Reprint requests to: J. D. Bernard, M.D., San Joaquin General Hospital, Post Office Box 1020, Stockton, Ca. 95201.

TABLE 1.—Some Clinical Features in Six Cases of TPP

Case	Age	Sex	Affected Muscles	Endo.	Duration of Sx Paralysis	Ethnic Background
1	27	M	legs → gen.*	0	4 y.	Japanese
2	26	M	legs	6 mos.	1 mo.	Mexican-American
3	18	M	legs → gen.*	0	2 y.	French-Filipino
4	19	M	legs	1 y.	2 da.	Spanish-Filipino
5	36	M	legs	3 mos.	5 mos.	Mexican-American
6	30	M	legs → gen.*	0	3 mos.	Mexican-American

*Sparing eye motion and breathing

TABLE 2.—Thyroid Function in Six Cases of TPP

Case	Clinical Hypermetabolism	PBI μgm. %	T ₄ μgm. %	RAI (%) 6 h.	24 h.
1	Slight	12.7	10.6	78	69
2	Moderate	10-12.2	—	32	22
3	Moderate	14.3	—	48	61
4	Marked	21.6	—	63	72
5	Only weight loss	16.0	17.2	—	32
6	Moderate	16.8	15.2	37	50
Normal Range:		4-8	3.2-6.4	8-15	11-25

On physical examination blood pressure was 140/74 mm of mercury and the resting pulse 96 beats per minute. There was slight eye prominence but no lid lag or exophthalmos. The thyroid gland was diffusely enlarged to twice normal size. The hands exhibited a fine tremor, and the skin changes of hyperthyroidism were noted. Serum potassium determinations between paralytic attacks were normal. Results of thyroid function tests are shown in Table 2.

The patient was treated with propylthiouracil for approximately 17 months but difficulties in controlling the disease ultimately necessitated thyroidectomy. The histology revealed changes characteristic of treated toxic goiter. There have been no further episodes of paralysis.

Case 3. An 18-year-old man of French-Filipino ancestry was admitted with the chief complaint of profound muscle weakness for 24 hours. This developed in the early morning hours and, upon waking, he was unable to move his extremities. He was transferred to the hospital, where examination disclosed absence of muscle stretch reflexes and paralysis of extremities; noteworthy were absence of respiratory difficulty and ocular palsy.

Because of a history of increasing nervousness, the patient was thought to have a conversion reaction and was transferred to the neuropsychiatric ward. Over several hours, there was gradual disappearance of the paralysis. The admission serum potassium was 1.7 mEq per liter, and several hours later it rose to 4.5 mEq without any therapy.

Further questioning revealed that, at age 16, the patient had noted the first episode of weakness, lasting approximately five minutes. Three or four episodes of brief duration produced weakness so profound he could not walk. Some episodes followed moderate exercise; others had no known precipitating cause.

When the family history was taken, it was found that a maternal aunt at age 47 had episodic leg weakness thought to be associated with low serum potassium levels; repeated attempts at verification through the patient's physician have failed. There was no other family history of thyroid or neuromuscular disease.

On reexamination the patient's resting blood pressure was 140/80 mm of mercury and pulse rate 126 per minute. The thyroid gland was enlarged. Mild tremor of the outstretched hands and fingers was noted. The laboratory evaluation is summarized in Table 2. A test to provoke hypokalemia and neuromuscular changes^{5-7,12,13} consisted of giving 150 grams of glucose intravenously over a 90-minute interval plus 20 units of regular insulin subcutaneously and 1 ml of 1:1,000 aqueous epinephrine subcutaneously. The results of this test are presented in Table 3. The test was terminated by intravenous infusion of 80 mEq of potassium chloride in 5 percent dextrose solution. Note in Table 3 that significant hypokalemia continued for several hours after the strength and reflexes returned to normal.

TABLE 3.—*Provocative Test for TPP in Case 3*

Medication	Time h.	Serum K ⁺ mEq./L.	Paralysis	Reflexes
s.c. epinephrine	(0	—	0	Normal
s.c. insulin	(½	3.6	0	Normal
i.v. glucose	(1½	1.9	Slight (legs)	Normal
-----	2	1.4	Moderate (legs)	Reduced
	(2½	1.3	Severe (legs)	Absent
	(Moderate (arms)	
i.v. K ⁺ in glucose	(3½	—	Slight	Absent
	(7	2.3	0	Reduced
	(9	3.4	0	Normal

Normal Range: 3.6 - 5.5 mEq./L.

Propylthiouracil therapy was used for the next several months, and later subtotal thyroidectomy was carried out. The histologic features were consistent with treated hyperthyroidism. Hypothyroidism subsequently developed and the patient is currently being treated with sodium l-thyroxine. There have been no further episodes of paralysis.

Case 4. A 19-year-old man of Spanish-Filipino extraction noted palpitations, nervousness, heat intolerance, increased appetite, and pronounced weight loss one year before hospital admission. He also noted neck swelling and muscle pain and weakness which resolved spontaneously. Two days before admission he had a nocturnal episode of weakness that began with muscle aching of the legs. Examination at the emergency room showed hypoactive reflexes, and the patient could not move his legs. There was no concomitant respiratory or ocular muscle weakness, and arm strength was normal. A serum potassium determination was 3.1 mEq per liter at this time.

The family history revealed that the patient's mother had a goiter in 1945, treated with thyroid hormone.

On physical examination on the ward two hours later blood pressure was 140/60 mm of mercury, and the pulse was 120, regular and bounding. The patient could now move his legs and active reflexes were present, with a rapid return component. Bilateral proptosis, warm, moist skin, hyperkinetic behavior, lid lag, stare, and scleral injection were noted. The thyroid gland was approximately three times normal size and a bruit was noted.

On laboratory evaluation basic studies, including an electrocardiogram, were within normal limits. Thyroid function studies were abnormal (Table 2) and studies of aldosterone excretion, serum electrolytes, and plasma glucose were within normal limits. A gastrocnemius muscle biopsy showed no abnormality.

On the third hospital day, induction of paralysis was attempted with intravenous glucose and insulin. No changes in reflexes or serum potassium levels were noted, and no weakness was induced. During the evening, however, leg aches developed and the patient could not walk for a half hour. A serum potassium determination was not obtained then; the following morning it was normal.

The patient was subsequently given radioiodine. Hyperthyroidism and muscle symptoms have disappeared and he is currently asymptomatic.

Case 5. A 36-year-old Mexican-American truck driver was well until five months before admission when he noted the onset of cramping calf pains and leg weakness on rising in the morning. During the three months preceding admission he lost 25 pounds. The day before admission, the patient awakened with leg cramps and weakness. He fell when he tried to stand, and was unable to move his legs for several hours. When seen in the emergency room the weakness and incapacity were so much improved that he was not admitted. Serum potassium at that time was 2.2 mEq per liter. He returned to the emergency room the following day with continuing complaints of weakness and leg cramps and was admitted for further study.

The family history revealed only the presence of diabetes mellitus. On physical examination the blood pressure was 160/80 mm of mercury and the pulse rate was 100 beats per minute. No objective findings of hypermetabolism were noted other than a rapid reflex return time.

Laboratory evaluation revealed normal serum electrolytes; thyroid function is reported in Table 2. An attempt at induction of hypokalemia and paralysis was unsuccessful.

Shortly after discharge, further episodes of weakness occurred, and a therapeutic dose of radioactive iodine was administered. When the patient was seen subsequently, symptoms and

signs of hypothyroidism had supervened. The patient was vastly improved, however, and denied muscle cramps or weakness.

Case 6. A 30-year-old Mexican-American man presented with acute paralysis. For approximately three months he had had episodes of weakness in the legs and arms. None of the usual complaints related to hyperthyroidism were noted. He had awakened from sleep the evening of admission, walked to the bathroom, and was unable to walk back to bed because of weakness of the legs. This progressed to total paralysis of the arms and trunk as well, except for the respiratory muscles.

In the emergency room, examination revealed inability to move the legs, but the patient could move his arms and was able to sit up in bed. The reflexes in the legs were decidedly hypoactive. Serum potassium at the time of admission was 2.1 mEq per liter. Examination several hours later revealed no weakness. Serum potassium four hours after the initial determination was 4.2 mEq per liter.

Family history revealed only that the patient's father had had one episode of "paralysis" years before, lasting but a short period. There was no history of known thyroid disease.

On reexamination, resting blood pressure was 140/80 mm and the pulse rate 102 beats per minute. On examination of the eyes a mild stare and minimal lid lag were noted. The thyroid gland was diffusely enlarged. There was a tremor of the outstretched hands, and skin changes typical of hyperthyroidism were observed. No evidence of muscle weakness, wasting or fasciculation was noted and the reflexes were normal. An electrocardiogram at the time of his hypokalemia showed non-specific ST-T changes compatible with hypokalemia. Results of thyroid function studies are shown in Table 2. An attempt at induction of paralysis was unsuccessful; no spontaneous episode of hypokalemia or paralysis occurred during the stay in hospital.

Several weeks after institution of propylthiouracil therapy, there was pronounced clinical improvement. No further episodes of weakness occurred in a five-month follow-up.

Discussion

The history and findings in these cases are typical of thyrotoxic periodic paralysis (TPP):^{1,2,4} nocturnal paralysis is common; daytime attacks

tend to follow exercise and large meals; weakness develops first in the legs, and generalization never paralyzes eye movements or breathing; paralysis can sometimes be induced for study by administration of glucose and insulin;^{5-7,12,13} clinical signs of hyperthyroidism may be mild or absent (Tables 1, 2), but laboratory tests reveal the endocrine disorder (Table 2); cure of the thyroid disorder also cures the paralytic attacks. The predominance of males noted in larger series^{3,4,5,7} also obtained in our six cases (Table 1).

In contrast to familial hypokalemic periodic paralysis, there is no significant family history in TPP, and the age of onset is at least early adulthood, the youngest in our group being 16 years of age (Table 1). Reviewing the world literature on TPP through 1959, Engel⁴ found that 90 percent of patients are 19 years or older at the onset, whereas 90 percent of patients with the familial disease are younger when symptoms begin.

The induced attack in Case 3 herein reported disclosed a disparity between the paralysis and the hypokalemia, a feature which has been noted recently by others.¹¹⁻¹³ In this patient, the strength recovered fully after the induced attack while significant hypokalemia continued (Table 3). Thus, the hypokalemia cannot be the sole or primary cause of the weakness. The cause is clearly hyperthyroidism, but the pathophysiologic mechanism causing paralysis remains obscure.^{11,12}

The myocardium is not involved in the paralytic biochemical disorder in TPP: any electrocardiographic alterations simply reflect the degree of hypokalemia (for example, Case 6). In view of the patient's extreme sensitivity to the provocative test in Case 3 (Table 3), it would seem wise in future cases to monitor the electrocardiogram frequently during such a test and to have a potassium ion infusion ready for use. This may not terminate the paralytic attack¹⁴ or even restore a normal serum potassium level (for example, Case 3, Table 3), but will provide sufficient potassium ions to protect the heart if necessary. The unsuccessful provocations in Cases 4, 5, and 6 indicate that, compared with careful clinical observations and the laboratory tests of thyroid function (Table 2), provocative tests have little diagnostic value despite their importance for research studies.¹¹⁻¹⁴

The major new finding from our series is the significant number of patients having Mexican ethnic backgrounds. West Coast physicians are probably alert to the possibility of TPP in Japanese or other oriental patients. Although small, this series indicates that TPP should also be considered strongly in Mexicans and Mexican-Americans who present with flaccid weakness, particularly older teen-age and adult males, even when clinical evidence for hyperthyroidism is minimal or absent (Tables 1 and 2). The two Filipino-Americans in this group, although only the second and third TPP patients with Filipino ancestry in the literature, indicate that this ethnic background may also predispose to TPP.

Summary

Six patients with typical thyrotoxic periodic paralysis (TPP) are presented. In contrast to previous reports, only one had oriental ancestry; three were of Mexican family origin and each of two had one Filipino parent. Nocturnal paralysis in a man with evidence of hypermetabolism should alert the examining physician to the possible diagnosis of TPP. This form of treatable periodic paralysis must be given special consideration in the emergency rooms of hospitals in the

southwestern United States where Mexican-Americans are treated. The signs and symptoms of hyperthyroidism may be mild or absent and laboratory studies of thyroid function are the most helpful aid to the diagnosis. Both the hypermetabolism and the paralytic attacks are cured by the appropriate anti-thyroid measure.

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LETTERS *to the Editor*

Medical Care, Health Care, and the Social Scene

A Mini-Symposium

To the Editor: The time has come to see what mechanism might be developed to implement the truism that "health care is more than medical care."

In developing these ideas, it is necessary that one's own bias be explained, at least in terms of definition. Under the phrase "medical care" I would list those things that the medical team does. By the medical team, I mean the physician, the nurse, the hospital and its myriad structures and all of the allied medical groups such as social workers, physiotherapists, inhalation technicians, the entire gamut of individuals who are, at this time, engaged in what is generally considered medical care. The activities of these individuals, by and large, tend to fall into the care of the sick and certain preventive activities; such as immunization procedures, periodic medical examinations and personal health education. This latter is generally given either in the form of formal lectures to large groups or some other teaching mechanism, or in the person-to-person advice that is given by health providers, be they physician, nurse or the like. To all who work on the medical team it is apparent that good health relates not only to the activities of this team but to other factors in life that one might call a larger health system. This health system contains matters of food, housing, transportation, religion, family life, employment, environment,

national survival, income, and "law and order." There are others that one can add to this.

It has become almost platitudinous for individuals attempting to improve medical care in deprived areas, to feel that the situation is rather hopeless unless these other aspects of health are addressed. Health statistics relating to incidence of disease, infant mortality, early premature death of adults, are perhaps related more to some of the latter health factors than of the activities of the medical team. We are now engaged in a great national debate to develop a system to distribute more equitably the costs of medical care. This debate is accompanied by a searching analysis of the need to develop more efficient mechanisms for delivering medical care and particularly for addressing those things that one considers preventive care. A problem related to this—and which seems of equal, if not greater, importance—is that of developing better linkages between medical care, health care and the larger social scene. Some present linkages might be thought of as follows:

- The role of the present medical team members when they're acting simply as citizens. Their activities in politics, and the personal impact that they can bring to bear on other bodies to promote their own interests. This role is undoubtedly a large one, and an important one, in terms of bringing to the various social agencies in our country, some of the need for alterations in their activities in order to promote better health.

- A second linkage has to do with the actual role of certain members of the medical team who come into somewhat closer linkage with larger health problems. One might list those en-

gaged in public health work, for they certainly have a great deal to do with problems of transportation, housing, and the like; perhaps among all members of the medical care team social workers are most likely to see the large impact of health care factors on an individual patient and his problems. Another example is the community psychiatrist who is engaged in looking at some of the organizational and functional problems of the community as they relate to the individual.

- Other linkages pertain to activities of groups other than the medical team, such as law enforcement agencies and their involvement with drug problems, alcohol problems, traffic injuries and the like; religious bodies and counselling groups; the food industry and appropriate governmental agencies such as the Department of Commerce, the Department of Agriculture, and those agencies responsible for standards of cleanliness and quality of food production; the building industry, and appropriate governmental political bodies such as Housing and Urban Development, and those individuals within it responsible for standards of construction; the ecologists and the growing demand for developing and enforcing safety standards for pollution; political agencies and insurance groups concerned with payment mechanisms for medical care.

All of these groups engage in activities which relate in some way to medical care and health; none of the non-medical groups feel that they have a responsibility for health statistics.

I would propose that what is needed is a serious effort to develop new linkages and to strengthen old ones so that health statistics might be shared as goals and objectives by other than just the medical care team. There are some ways in which this might be accomplished. On the one hand, there is a growing concern that all health matters should be under the control or jurisdiction of a Department of Health, that within this would come all of the activities relating to health, not only medical but those other activities mentioned. This is epitomized to some extent in the arguments that have gone on between the Department of Health, Education, and Welfare and the Attorney General's office as to which department should have jurisdiction over drug abuse. One can certainly speak, with a certain amount of validity, to either point of view. I would like to propose, as an alternative, a dis-

persal of health responsibilities to many social agencies, rather than a removal of these responsibilities from them and the concentration of these into one so-called Health Department. If we are to have better housing; if we are to have adequate transportation and adequate nutrition; if we are to realize the impact on health of employment and unemployment; these matters should not remain the purview of a "health care" or a "medical care" department but all of society should be involved. I would suggest the following examples as types of dispersal that might be considered in order to improve the health of the nation and to impress the responsibility for health matters upon many different agencies:

- All sanitation standards and inspection of public and private housing should be invested in a Department of Housing. This department should be required, with proper consultation, to develop and implement these standards.

- Programs for mental health, particularly as they relate to aberrant social behavior, drug abuse problems, alcohol problems, should be moved into a joint activity with justice and legal agencies.

- Departments and Divisions of Public Transportation should be given the responsibility for developing and analyzing the health needs in the area of transportation.

- Public bodies under present regulatory agencies should be set up to franchise emergency care; to set standards of performance. The management of emergency systems should be a responsibility of either a Fire or Police Department.

- The food industry and the Department of Agriculture should be given the responsibility for appraising and developing the nutritional needs of the nation.

The role of a Health Department in this should be the coordination of these activities and the continuous dispersion of such activities into appropriate social agencies. In our system of government, with its multiple, pluralistic, autonomous and individual activities, it does not seem appropriate to have an isolated health system or Health Department; instead, those criteria by which we judge the physical and mental health of our nation would become responsibilities of many and various public bodies. When national political leaders use health statistics, such as infant mortality, early death of middle class males,

spread of disease amongst the poor, as arguments for payment for medical care, it implies a lack of recognition of the very large, if not primary, role that other national activities play in the production of these statistics. Until it is politically and socially recognized that medical care is but one aspect of health, and that the creation of mechanisms for financing of medical care are not only an incomplete but possibly a wrong solution, will we begin to affect significantly some of the statistics that have been bandied about so easily.

DONALD W. PETIT, M.D.
Alhambra

‘ ‘ ‘

To the Editor: In the preamble of the constitution of the World Health Organization is an articulate, all-encompassing definition of health, namely, "Health is a state of complete physical, mental and social well-being, and not merely the absence of disease or infirmity."

I doubt that such a broad, and all-inclusive definition is realistically achievable today. Certainly it has not been accepted by all concerned, but it should serve as a challenge and be looked to as an ultimate goal.

The House of Delegates of American Medical Association in 1970 approved a definition that seems more realistic: "Good health is a state of physical and mental well-being."

As both definitions imply medical care truly is only one part of health care. It is the physician who is totally responsible for the former. Practically speaking health must be qualified by description because one may have poor or bad health. Most people don't realize the meaning of good health and many take it for granted. Only when it is lost can one appreciate its true meaning.

Health care will be a major issue in the 1972 Presidential election. Those of us in the private practice of medicine find ourselves in an unfortunate position of prominence because of this social problem.

Let us all—physicians, politicians, social planners, educators and others—remember that it is only the physician who can scientifically treat our people. But solutions toward improving the health care of our people must be shared between the private sector of society and govern-

ment, and the components of the developing health teams. This joint input and balance will improve the effective delivery of a pluralistic health care system in the United States.

I do not intend to add to our welter of semantics, but in a very real sense there is even confusion in defining health and health care services. It appears that we as physicians are often guilty of this mistake. Health may be good or bad, and it is a physical, mental or social state dependent on genetics, environment, personal habits and health care services.

We hear a great deal about the "health team." Actually the health team is only a concept, and it is really not new. Our medical care system has always been built on teamwork, and a division of labor as evidenced by a steady increasing interdependence among professionals. The ever-increasing specialization of medical practice, a system of referrals, the use of consultants, as well as the interrelationship between the medical profession and members of the allied health professionals exemplify a team effort that maximizes available resources. Additional components of a cooperative approach are typified by allied health professionals in hospitals, the voluntary health workers, social and public health agencies.

The neighborhood health center is a primary experimental location for the operation of health teams, because the center is established to deliver a full range of health care services in a comprehensive and continuous manner in specific areas. In an effort to foster the health team concept, a coordinated interdisciplinary approach for the education and training of allied health personnel is being attempted by a number of universities throughout the country.

It appears that the health team will develop pretty much along the lines of the traditional individual health care services: The acute and intensive care teams; the extended care team; the rehabilitation and restorative teams; the more recently advocated disease prevention and health maintenance teams, and finally those teams dealing with the environmental aspects and ecology of health.

So it is in this context that "Health care is inescapably a community effort calling for comprehensive health services for everyone and, a personal physician who will provide the continuity of integrated medical and medically-related serv-

ices," as the National Commission on Health Services said in a report titled "Health Is a Community Affair."

It is imperative that a correct and proper evaluation and understanding of health care vs. medical care be developed. Medical care is a basic component of health. It represents the services performed by the physician, and those provided by allied health personnel under the direction of the physician and for which the physician is responsible.

In contrast, health care is a broad social responsibility involving the availability and accessibility of medical services provided in hospitals and other facilities. Personal hygiene and habits, housing, environmental pollution, sanitation, education, planning, food and nutrition, transportation—or the lack of such elements—constitute and affect the health care of a nation. One may then conclude that the responsibility for medical care is indeed that of the physician. But the social planner, the educator, the environmentalist, the public health worker and many others share in the associated responsibility for health care.

This of course leads to accountability of medical services and resultant statistics. For this the physician is also responsible. But when we consider health statistics, these are as much the responsibility of others.

This then leads to the current and perhaps improper trend to assess a nation's health system through statistics. It is here that I take issue.

To the practicing physician one of the most sensitive examples of misuse of statistics has been the attempt to use infant mortality figures as a basis for the assessment of our nation's health. We see such figures used as an index purporting to indicate the comparative state of our nation's health.

The variables in infant mortality and life expectancy are more symptoms of low economic conditions and cultural patterns than of the level of medical care provided.

It is unfortunate that in the United States such comparative statistics have often been used politically, comparing American mortality and longevity rates with those of other nations for less than scientific purposes.

Infant mortality is truly more a social than a medical problem. Such factors as poverty, malnutrition, poor housing, inadequate sanitation,

low educational levels, and ethnic and cultural differences are more closely associated with infant mortality than are the number of doctors and hospitals or the level of care they provide.

When we consider that 70 percent of the deaths in the United States are related to cancer, heart disease and stroke, and only 2.2 percent of our deaths are due to infant mortality, the significance of the latter can be seen in its true perspective.

It is not generally stated, but comparisons of the United States' with Sweden's infant mortality is usually meant to imply that the United States system is deficient and we should adopt the Swedish health system. Since this is the most common comparative reference, it is interesting to examine other areas.

- Sweden has a population of eight million and the United States two hundred and five million.

- The United States covers 3.6 million square miles; Sweden about the same as our state of California, 175 thousand square miles.

- Sweden has an homogeneous population, the United States an extremely heterogeneous population by all measurements—ethnic, social, cultural and economic.

- The infant mortality rates in Minnesota and Wisconsin, where there is a high population of Swedish descent, are lower than Sweden's.

- The World Health Organization's *Demographic Yearbook* makes note that the figures *should not be used for comparison* because standards of measurements vary with nations.

In most countries, reports of births are the responsibility of parents, and since there is no punishment for not registering, a sizable percentage of infant deaths go unrecorded. In the United States the physician is responsible for certifying all births and deaths, and our criterion is "one heart beat is a live birth."

So if we were to use the same statistical source that Senator Kennedy used in speeches across the country, the United States could be said to have the best health care system because we had the lowest death rate due to bronchitis. France, too, could be said to have the best, because it had the lowest incidence of deaths due to peptic ulcer. And the Netherlands also could be first, for its death rate due to tuberculosis and pneumonia is lowest.

The point is that we must avoid a mix of

apples and oranges, particularly when we discuss a subject so important as the health of Americans.

A profound interest of the medical profession is that it have a system in which physicians can continue to provide the best possible medical care for all the people.

MALCOLM C. TODD, M.D.

*Chairman,
CMA Comprehensive Health Planning Committee
Past President, CMA
Long Beach*

1 1 1

To the Editor: Medical care, no matter how fine, comprehensive or responsive to equity needs, as well as speed of response, quality or efficiency, no matter what the cost, will not affect the health of Americans. Health is not the concern nor prime province of the medical profession, save in rhetoric and in preambles to legislative action.

Neither medical care nor health is solely the responsibility of the physician. Indeed one might historically (in an outlined form) trace the evolution of concern:

- The patients' cry of "I hurt" led to many persons of different bent responding to the cry.
- The physician, of all these, earned the right to intervene and respond to the cry.
- Science and technology increased the competence of the physician and his medical allies.
- At the same time, medical care became more complex and fragmented. More and more individuals and groups became involved in the professional arena.
- As society demonstrated that it could cope with meeting human needs of all kinds, aspiration levels increased.
- As the concepts arising from medicine's and society's complexity evolved, models of behavior became more and more concerned with interactions and transactions, ecology and social systems.
- Health became differentiated from medical care. Thus as the complexities of health become clarified, it is more obvious that it is related to the broader social issues: employment, poverty, housing, environment (physical and social) and innumerable other factors. It is not the absence of illness but is more closely related to the well-being of man and the quality of life.

• Since society had previously legitimized the physician's role in medical care, as health became a concern "in good currency," it transferred at the least the "rhetorical responsibility" to him without giving him the resource tools or real responsibility to perform.

• Medicine has from its perspective chosen to remain responsible for medical care, and *not* be involved in health.

What, then, is society demanding? A profession modifies and changes both as a result of internal developments (science, art and technology) and from society's pressures, emerging out of a vast number of social changes.

The increased aspiration by people for medical care reflects many things: increased communications, affluence, scientific development and the need to correct inequities of quality and the availability of care. Demands escalate as we demonstrate through research, or care of a few people, how high the quality of care by the medical profession can be. But the very complexity and fragmentation, in part stimulated by our national support system, provokes frustration in both physicians and patients. We all want a better job done.

The current demands for more money and national insurance avoid the key questions:

- How do you meet diverse demands and expectations of medical care to lower death rate, decrease morbidity, reduce disability, dissatisfactions and discomforts? Each group in the medical community, including the patients, has different priorities.
- Are there ways to deliver medical care by developing new systems — for example, group practices, ambulatory health centers, emergency services?
- Can the poor be brought truly into the mainstream of medicine and given first quality care, without excessive costs to consumers, providers or their party payers?

Society has taken a pre-Copernican position—if you deal with finance, all else will follow. This is not so.

To this end in a recent report to the Science and Technology Advisory Council of the State Legislature [of California] I supported the development of a pattern of local health authorities where *all* those involved in medical care

(including patients) can in one place not only plan (as in Comprehensive Health Planning) but develop mechanisms for delivery of care through the private and public sector (for example, local mental health authorities). Further, that choice of models of care be open to the providers and to the clients; a competitive system of insurance (pre-paid/capitation or fee for service) and competitive modes of organization (private practice, groups, hospitals, HMO's, neighborhood health centers).

Upon this framework of localizing the solutions should be built a State Health Authority which brings together *all* medical care findings, regulatory programs, and licensure that is responsive to local demands and expectations. Within this structure, whatever finance or insurance system develops would then have the opportunity to be maximally responsive rather than funding "the same old thing" (money down the drain).

My call is for medical leadership to face up both to our own parochial needs and demands and the broader needs as well. I would hope we can do so and, in a collegial relationship with other groups, concern ourselves with systems of care that meet the multiple expectations and demands of society.

The broad world of health demands that we as physicians direct the attention of society toward the source of some of the causes of illness. Can we assume, in addition to our care responsibility, a Ralph Nader-like role of "conscience" in health related areas? Sad to say, health concerns are low in the priority of values, in the basic decision-making of our society. It would seem to be our responsibility—as some of our young physicians have reminded us—to change these priorities. Further, we must show that the health of the nation *cannot* be the responsibility of the medical profession but must be that of society at large.

Illness can then be viewed as a signal that other issues are present. The signal suggests a two-pronged approach toward finding out what has gone wrong with the patient's internal ecology; or to finding out what in the environmental ecology has caused the disorder.

Medicine has classically taken the former approach, and despite some of the current problems of delivery has made a major impact on individual illnesses.

What this speaks to is that the important direction ahead of us is in the redefinition of what has been public health. The public's health is related to our concern with the physical and social environment. It becomes a concern with the quality of life and human well being—with the values we hold (not in rhetoric but in decision-making) and the priorities we use in allocating our resources. It becomes a concern with politics, planning, participation (the more one participates in solutions to one's own problems, the more one has a sense of competence and well-being, and thus, health) government, and management—not just of medical areas but of all those areas which make up the urban scene.*

The responsibility for much of what is health thus lies outside our profession—with input from us as citizens, professionals, and most often as co-equal colleagues.

LEONARD J. DUHL, M.D.

*Professor of Urban Social Policy and of
Public Health
Department of City and Regional Planning
University of California, Berkeley
Professor of Psychiatry
University of California, San Francisco*

1 1 1

To the Editor: In one November editorial [The health care team. Calif Med 115:54-55, Nov 1971] you ask a provocative question and in another [Medical education in transformation. Calif Med 115:53-54, Nov 1971] you make a provocative statement. Both editorials suggest response.

In discussion of the health care team, you conclude with the statement that the physician must fit himself into such teams. I should like to question the appropriateness of that statement. Events have demonstrated that the role of the physician is widely misunderstood—even by physicians. There has been little attempt to make a clear-cut separation between the function of the physician and the function of all others in the so-called health team. In newspaper accounts and in public discussion both are lumped into something variously and indiscriminately called medical service, medical care, health service, or health care. Since there is a highly significant difference between what the

*See L. J. Duhal: *The Urban Condition*. New York, Basic Books, Inc., 1963

physician does and what is done by all others on the team, we should try to make the difference clear by referring to *medical care* and *health service* as what they actually are.

By referring to the activities of physicians as *medical care*, and the activities of others in the health field as *health service*, we can clarify thinking about the important problems facing the profession and the nation. The physician, therefore, should not try to become a member of the team, as stated in your editorial, but must accept the responsibility of being its leader. History of all organized activities indicates that leaders must always be distinguished from those being led, no matter how closely they may work together.

Your question in the preceding editorial on medical education concerns the direction it is taking. Where is it going? No one can answer the question but before the attempt is made there should be some understanding of what we are talking about. Clarification here is the distinction between *education* and *training*. It is impossible for any medical school to prepare any person for the practice of medicine for any given time after graduation. Medical education should *not* be preparation for practice. Training for function in the real world comes later. The words *training* and *practice* are closely related and they are distinct from *education*.

The brain of the medical student should not be considered merely as a receptacle for a large number of facts. It should be considered an instrument having the ability to recognize the significance of facts when they are obtained. True, the instrument must have a memory bank of facts of permanent value, but it must be ready to integrate newly acquired facts with the basic material and come to an intelligent conclusion.

This means, of course, that education in a medical school is a mind developing process and is only an introduction to education that must continue throughout life. The total volume of fact to be acquired after graduation far exceeds anything that can be crammed into the brain of the medical student before he graduates. Education, then, becomes a continuing process. The physician, in this process, and only in this process, is distinguished from other members of the team by being a member of a learned profession.

HERBERT L. HARTLEY, M.D.
Editor
NORTHWEST MEDICINE

An Unexpected Protest

To the Editor: I am enclosing a copy of an unexpected protest letter received from the young daughters of a patient whom my partner had just placed on a weight reduction regimen as an aid in reduction of mild hypertension. I believe the charm of the youngsters' note speaks for itself.

HAROLD M. COHEN, M.D.
Sylmar

Doctor radley,
We don't want our Mother on a diet. We want a fat Mommy. So she will Look like a Mommy and more to hug.

The _____ girls.

Coronary Arteriography

To the Editor: In the Vol. 115, No. 5 November issue of CALIFORNIA MEDICINE, Dr. Selzer et al presented the lead article concerning indications for coronary arteriography. An assumed association between caseload and risk of coronary arteriography is implied throughout the article, however, the figures may be somewhat misleading. His statement that no statistical analysis of the figures concerning the rate of complications is necessary *should read* "is possible." He associates one institution supplying 2,700 cases with other institutions supplying 600 cases. Although the totaled complications of the latter institutions was 6.1 percent, what were the individual institution percentages? As an example, if two hospitals were represented, one could have a 1 percent complication rate and the other an 11.2 percent complication rate, giving an average complication rate of 6.1 percent, however, one institution has a much lower complication rate and conclusions from this type of survey would be difficult at best.

Also, it should be remembered that some institutions have several cardiologists performing

cardiac and coronary angiography with varying individual caseloads and yet from my observations in community hospitals there have been little differences in complication rates among the individual physicians.

Looking at Table 1 of the article, hospital A with the largest caseload has over 100 percent increase in deaths from coronary angiography (seven deaths), compared to hospital B (three deaths) with only 50 patients less than hospital A. The percent death rate is obviously higher (1 percent) in hospital A than hospital B (0.5 percent). Selecting figures necessary in making a point can be misleading and impart unjustifiable conclusions. If we look for a common denominator, we arrive at a situation which is similar to that seen in institutions performing cardiac surgery. Some teams have a high patient mortality rate while others have a relatively low mortality rate. Two factors which could account for this are the physiological status of the patients at time of intervention and the competence of the operator. In performing 126 coronary angiographic procedures in a three-year period in a community hospital, we have not had any mortality or serious complications attributable to the procedures. It would seem unlikely that for no apparent reason we should now anticipate a sudden increase in morbidity and mortality. I know of other cardiac catheterization laboratories in community hospitals performing less than 200 procedures in a three-year period with no mortality. Thus, one must avoid the temptation to generalize on the risks involved in performing specified procedures unless all the variables are known. I know of no invasive procedure which is without risk however the possible complications must be anticipated by the cardiologist and, more important, he must be able to recognize and immediately treat these complications. If the individual performing coronary angiography has the skills and knowledge necessary, the overall risk-rate should be quite low.

GEORGE L. KEMP, M.D.
*South Coast Community Hospital
South Laguna, Ca*

1 1 1

The Authors' Reply

Dr. Kemp's letter raises the point of reliability of statistics regarding morbidity and mortality from invasive diagnostic procedures. The ques-

tion concerning the rate of complications raised by him cannot be answered by us, since we merely cited results of the Cooperative Study organized by the American Heart Association. These questions should be directed to Drs. Richard Gorlin and Richard Ross, who reported on coronary arteriography aspects of that study. In regard to Table I of our article, it was not intended to be a statistical study but was merely an illustration of the higher risk of the procedures performed in institutions with a low caseload. We are pleased to know that there are institutions that can beat even the Cleveland Clinic by showing no mortality at all and no complications. Perhaps that indicates the attainment of supreme skill in the performance of coronary arteriography; perhaps it indicates luck. One could raise another point: in a community hospital (by definition not a referral center) the performance of one or two coronary arteriograms per week suggests that more such procedures are being done than are indicated by currently accepted criteria. The inclusion of many good-risk patients, who do not need a test or an operation in the first place, is a recognized factor favorably affecting statistics both in invasive diagnostic procedures and in cardiac surgery.

Recently, one of our colleagues who is designing laboratories for the new Presbyterian Hospital, now under construction, has visited 12 major cardiac centers throughout the country; he has yet to encounter such an institution that has a record of performing coronary arteriography or comparable arterial retrograde procedures, without mortality and morbidity.

I wish to emphasize that our article did not express solely the opinions of the authors: it reiterated and amplified the official recommendation of the Inter-Society Commission for Heart Disease Resources in which the leading experts in the field stated: "Three hundred cases per annum is recommended as a minimum number required to maintain the expertise of the professional team engaged in these highly complicated procedures." It is quite clear that coronary arteriography does not belong in the community hospital, but in a complete cardiac center with an adequate caseload.

ARTHUR SELZER, M.D.

WILLIAM L. ANDERSON, M.D.

HAROLD W. MARCH, M.D.

*Presbyterian Hospital and
Veterans Administration Hospital,
San Francisco*

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PUBLIC HEALTH REPORT

Frederick B. Hodges, M.D., Chief Deputy Director, State Department of Public Health

Diethylstilbestrol: Problems of Unusual Drug Dosage and Administration

WHEN ANY SUBSTANCE IS suspected or established as a cause of cancer, it is a valid cause for alarm, especially when the carcinogen is an old, well-known drug. It is even more disheartening when the cancer is manifested in progeny one generation after the drug was originally administered, as is the case with diethylstilbestrol (DES).

DES has been recommended for years to treat symptoms of menopause in the usual doses of 0.2 to 0.5 mg daily. The current Physicians' Desk Reference (1971) lists the following additional indications: senile vaginitis, relief of painful engorgement of breasts postpartum, control of functional uterine bleeding, carcinoma of the prostate, and mammary carcinoma of postmenopausal women.

Once considered a major medical advance providing safe, effective, and low-cost estrogen therapy for these and other conditions, DES is now thought to be a carcinogen, on the basis of animal studies. It may not be added to chicken feeds or be present in beef for human consumption.

Recently, the *New England Journal of Medicine* reported that cancer of the vagina has been linked to DES. In the cases cited, the drug was administered during pregnancy that produced the child at risk, and the child was at puberty when the tumor was discovered. This fits the

basic biological concepts of carcinogenesis: the effects of carcinogens are dose-dependent, additive and irreversible; carcinogenesis requires time; the cellular changes that trigger it are transmitted to daughter cells; carcinogenesis can be influenced by factors that are not truly carcinogenic; and it requires cell proliferation.

Data from the California Tumor Registry of the State Department of Public Health for the period 1942 to 1968 were recently reviewed for all urogenital cancers, male and female. Since 1962 there has been an accumulation of cancer cases reported in the 10 to 19 year age group for several sites: vagina, testes, prostate and bladder. No such accumulation was seen for cancers of the breast, cervix, stomach, colon or rectum. These preliminary findings are being studied further by the California Tumor Registry staff and the California Cancer Surveillance Unit, headed by Dr. Brian E. Henderson at the University of Southern California.

In the light of these findings, it is dismaying to see in both the medical and lay press articles extolling the virtues of DES in uses and dosages not recommended in the labeling. The August 1971 issue of the *Skin and Allergy News*, for example, advises long-term, high doses (ranging from 10 to 7500 times the usual) for reducing sebum production and managing papular dermatitis of pregnancy, which has a reported 30 percent fetal morbidity. And the lay press frequently reports DES's extraordinary successful use as a "morning after" pill to eliminate the chances of pregnancy.

These developments point up some of the problems of medical communication. There is a great volume of medical literature, but what do we know about its quality? And how can we evaluate it? According to the California Bureau of Food and Drug, the law ostensibly protects readers of advertisements in medical journals from inaccurate and incomplete drug information, but

there is little protection for readers of "clinical experience" articles. Compare, for example, the requirement for "substantial evidence," "full disclosure," and "fair balance" in the labeling and advertising of drug manufacturers with the free rein that exists for presenting unilateral observations in a "scientific" meeting. The advocacy of DES in pregnancy, blood changes due to use of methotrexate in psoriasis, and visual damage from chloroquin in arthritis suggest the increasing need for a specialist to read beyond his specialty and to keep up with the best informed clinical pharmacology before prescribing any drug. This becomes especially important when the drug is offered for an unaccepted, although not unacceptable, use or in a decidedly unusual dosage or duration of administration.

Perhaps we need a mechanism to pool data concerning medical experience with unusual doses and utilization of existing drugs.



Selected Item from the FDA Drug Bulletin — November 1971

Diethylstilbestrol Contraindicated in Pregnancy: Drug's Use Linked to Adenocarcinoma in the Offspring

WE WISH TO BRING to the attention of all physicians, hospitals, and medical personnel an important possible toxic effect of diethylstilbestrol (DES) reported for the first time in April 1971 by Herbst et al.¹ From their studies the authors concluded that maternal ingestion of diethylstilbestrol during pregnancy appears to increase the risk of vaginal adenocarcinoma developing years later in the offspring exposed. The authors studied eight cases of adenocarcinoma of the vagina in patients born between 1946 and 1951. The malignancies were identified and treated between 1966 and 1969. In seven of the eight cases, there was a history of maternal use of diethylstilbestrol. Because this type of malignancy in young girls had rarely been reported previously,

the authors conducted a retrospective investigation in an attempt to find factors that may be associated with such malignancy in this age group. Four matched controls were established for each patient and the data obtained were subjected to statistical analysis. A statistically significant relationship was observed for three variables: diethylstilbestrol given during pregnancy ($p=.00001$), bleeding in that pregnancy ($p=\text{less than } .05$) and prior pregnancy loss ($p=\text{less than } .01$). It is obvious that the most significant of the variables is the administration of diethylstilbestrol during pregnancy.

Since publication of this study, five additional cases of this malignancy associated with the maternal use of diethylstilbestrol have been reported by Greenwald et al.² Dr. Herbst, in a recent communication to FDA, has reported an additional 15 cases associated with use of this drug, bringing the total number of known cases to 27. It must be emphasized that this type of epidemiologic study defines only an association and not necessarily a cause-and-effect relationship. Further studies are underway to clarify the significance of these findings.

In the meantime, the FDA is initiating the following precautionary actions:

1. All manufacturers of DES or closely related congeners (dienestrol, hexestrol, benzeestrol, promethestrol) are being notified that appropriate changes will be required in the labeling for such drugs. This change will consist in the listing of pregnancy as a contraindication to the use of diethylstilbestrol and the other above-mentioned compounds.
2. All other estrogens will be required to have the following WARNING in their labeling: "A statistically significant association has been reported between maternal ingestion during pregnancy of diethylstilbestrol and the occurrence of vaginal carcinoma developing years later in the offspring. Whether such an association is applicable to all estrogens is not known at this time. In any event, estrogens are not indicated for use during pregnancy."
3. Epidemiological studies are being initiated to determine the true incidence of this disease in young women, the number at risk, the characteristics of patient populations with this malignancy, and the probability of a cause-and-effect relationship.

Both FDA and the medical profession face a responsibility to help determine whether this reported association constitutes a cause-and-effect relationship. We ask that all physicians consider appropriate steps to assist FDA case-finding and to protect any patients who might be at risk.

It may be possible to trace the offspring of those mothers who received DES during pregnancy. All physicians should be especially alert for young women whose mothers may have received hormonal therapy during pregnancy, particularly those young women who may be experiencing irregular vaginal bleeding. The association should be a routine consideration for physicians whose practice includes young women.

This is a previously unsuspected health prob-

lem. Further information is essential to the FDA and to the medical profession. We ask your help in reporting any cases you encounter for entry in a case registry.

FDA will take every possible step to insure that you are kept abreast of new information as soon as it can be gathered and analyzed.

For your convenience, an adverse reaction reporting form is printed below. FDA will forward a supply of forms to each practicing physician as soon as they are printed. Facsimile forms are acceptable.

REFERENCES

1. Herbst AL, Ulfelder H, Poskanzer DC: Adenocarcinoma of the vagina: Association of maternal stilbestrol therapy with tumor appearance in young women. *New Engl J Med* 284:878-881, Apr 22, 1971
2. Greenwald P, Barlow JJ, Nasca PC, et al: Vaginal cancer after maternal treatment with synthetic estrogens. *New Engl J Med* 285: 390-392, Aug 12, 1971

DRUG EXPERIENCE REPORT (IN CONFIDENCE)			Form Approved OMB No. xxxxxxxx	
PATIENT INITIALS (Optional)			DATE OF REACTION ONSET	
SUSPECTED REACTION(S)				
SUSPECTED DRUG(S); TRADE/GENERIC NAME (Manufacturer's name, if possible)				
DISORDER OR REASON FOR USE OF DRUG(S) (Optional)	ROUTE	TOTAL DAILY DOSE	DATES OF ADMINISTRATION	
OTHER DRUGS TAKEN CONCOMITANTLY				
COMMENTS (Optional)				
PHYSICIAN'S NAME, ADDRESS, AND ZIP CODE				

FD PROPOSED FORM

In Memoriam

Persons wishing to do so may make contributions to the Physicians' Benevolence Fund to honor the memory of a member who has died. Members of the family will be notified that such a contribution has been made and the name of the donor will be supplied.

Checks should be addressed to Physicians' Benevolence Fund, Inc., California Medical Association, 693 Sutter Street, San Francisco, Ca. 94102.

AINLAY, GEORGE WILLIAM, JR., Los Angeles. Died November 21, 1971 in Santa Monica of cancer, aged 53. Graduate of the University of Nebraska College of Medicine, Omaha, 1943. Licensed in California in 1947. Doctor Ainlay was a member of the Los Angeles County Medical Association.

✱

ARTZ, D. DUANE, Reseda. Died December 20, 1971 in Canoga Park of leukemia, aged 50. Graduate of the College of Osteopathic Physicians and Surgeons, Los Angeles, 1951. Licensed in California in 1951. M.D. degree from California College of Medicine, 1962. Doctor Artz was a member of the Los Angeles County Medical Association.

✱

BOYD, E. FORREST, SR., Los Angeles. Died December 19, 1971 in Hollywood of complications following eye surgery, aged 82. Graduate of Stanford University School of Medicine, Palo Alto-San Francisco, 1919. Licensed in California in 1919. Doctor Boyd was a member of the Los Angeles County Medical Association.

✱

CAMPBELL, DONALD MCLEAN, San Francisco. Died July 25, 1971 in San Francisco of adenocarcinoma of the rectum, aged 76. Graduate of the University of Toronto Faculty of Medicine, 1923. Licensed in California in 1928. Doctor Campbell was a member of the San Francisco Medical Society.

✱

FUHRING, SHIRLEY A., Santa Maria. Died September 8, 1971 in Lompoc of carcinoma of colon, aged 64. Graduate of the University of Oklahoma School of Medicine, Oklahoma City, 1932. Licensed in California in 1957. Doctor Fuhring was a retired member of the Santa Barbara County Medical Society and the California Medical Association, and an associate member of the American Medical Association.

✱

GALLAGHER, ROBERT, Whittier. Died November 28, 1971 in Whittier of heart disease, aged 54. Graduate of the College of Medical Evangelists, Loma Linda-Los Angeles, 1951. Licensed in California in 1952. Doctor Gallagher was a member of the Los Angeles County Medical Association.

HALL, RAYMOND CONFER, San Diego. Died November 29, 1971 in San Diego, aged 86. Graduate of Johns Hopkins University School of Medicine, Baltimore, 1914. Licensed in California in 1929. Doctor Hall was a retired member of the San Diego County Medical Society and the California Medical Association, and an associate member of the American Medical Association.

✱

HARDGRAVE, LLOYD ELLIOTT, San Francisco. Died December 3, 1971 in San Francisco, aged 79. Graduate of the University of California Medical School, Berkeley-San Francisco, 1920. Licensed in California in 1920. Doctor Hardgrave was a member of the San Francisco Medical Society.

✱

HARRIS, LILY GUYSELMAN, Oakland. Died December 16, 1971 in Oakland of myocardial infarction, aged 88. Graduate of the College of Osteopathic Physicians and Surgeons, Los Angeles, 1923. Licensed in California in 1923. M.D. degree from the California College of Medicine, 1962. Doctor Harris was a retired member of the Alameda-Contra Costa Medical Association and the California Medical Association, and an associate member of the American Medical Association.

✱

JONES, KENNETH PAUL, Santa Monica. Died December 11, 1971 in Laguna Hills of cancer, aged 77. Graduate of the University of Michigan Medical School, Ann Arbor, 1923. Licensed in California in 1926. Doctor Jones was a member of the Los Angeles County Medical Association.

✱

LANDEGGER, GEORGE P., Los Angeles. Died December 25, 1971 in Los Angeles of cancer, aged 70. Graduate of Medizinische Fakultät der Universität, Wien, 1926. Licensed in California in 1932. Doctor Landegger was a member of the Los Angeles County Medical Association.

✱

LAWSON, JOHN DOWELL, Antioch. Died December 8, 1971 in Antioch, aged 76. Graduate of St. Louis University School of Medicine, 1920. Licensed in California in 1920. Doctor Lawson was a retired member of the Sacramento County Medical Society and the California Medical Association, and an associate member of the American Medical Association.

✱

McKAY, FRANCES M., Santa Cruz. Died November 20, 1971 in Pasatiempo (Santa Cruz), aged 58. Graduate of Creighton University School of Medicine, Omaha, 1938. Licensed in California in 1939. Doctor McKay was a member of the Santa Cruz County Medical Society.

MILLZNER, RAYMUND JOSEPH, San Francisco. Died December 14, 1971 in San Francisco, aged 70. Graduate of the University of California School of Medicine, Berkeley-San Francisco, 1926. Licensed in California in 1926. Doctor Millzner was a member of the San Francisco Medical Society.

✱✱

NELSON, JOHN MILLER, Laguna Hills. Died September 12, 1971 in San Clemente of coronary artery arteriosclerosis, aged 71. Graduate of the University of Minnesota Medical School, Minneapolis, 1928. Licensed in California in 1963. Doctor Miller was a member of the Orange County Medical Association.

✱✱

OECHSLI, WALDO RAYMOND, Los Angeles. Died December 20, 1971 in La Jolla of acute coronary occlusion, aged 89. Graduate of the University of Kansas School of Medicine, Lawrence-Kansas City, 1918. Licensed in California in 1926. Doctor Oechsli was a retired member of the Los Angeles County Medical Association and the California Medical Association, and an associate member of the American Medical Association.

✱✱

PERRY, CHARNA G., Sausalito. Died November 25, 1971 in Greenbrae, aged 77. Graduate of Tufts College Medical School, Boston, 1920. Licensed in California in 1923. Doctor Perry was a member of the Marin County Medical Society.

✱✱

RIGGINS, WINSTON CALAWAY, Long Beach. Died November 24, 1971 in Big Bear City of injuries received in a plane crash, aged 63. Graduate of the University of Arkansas School of Medicine, Little Rock, 1935. Licensed in California in 1951. Doctor Riggins was a member of the Los Angeles County Medical Association.

✱✱

SMITH, ALBERT EDWARD MELVILLE, Van Nuys. Died December 12, 1971 in Van Nuys of heart disease, aged 49. Graduate of the University of Oregon Medical School, Portland, 1946. Licensed in California in 1955. Doctor Smith was a member of the Los Angeles County Medical Association.

✱✱

SORAUF, BERNARD MAX, Fresno. Died December 16, 1971 in Fresno, aged 65. Graduate of the University of Colorado School of Medicine, Denver, 1931. Licensed in California in 1933. Doctor Sorauf was a member of the Fresno County Medical Society.

✱✱

TARRE, HAROLD I., Lakewood. Died December 10, 1971 in Long Beach, aged 57. Graduate of the University of Illinois College of Medicine, Chicago, 1940. Licensed in California in 1947. Doctor Tarre was a member of the Los Angeles County Medical Association.

✱✱

THOMAS, HENRY RANDALL, Los Angeles. Died November 17, 1971 in Studio City of cancer, aged 56. Graduate of the University of Pennsylvania School of Medicine,

Philadelphia, 1939. Licensed in California in 1946. Doctor Thomas was a member of the Los Angeles County Medical Association.

✱✱

THOMPSON, JAMES EUGENE, Newman. Died September 2, 1971 of coronary artery occlusion, aged 68. Graduate of the University of Colorado School of Medicine, Denver, 1928. Licensed in California in 1932. Doctor Thompson was a retired member of the Stanislaus County Medical Society and the California Medical Association, and an associate member of the American Medical Association.

✱✱

TROLINGER, JAMES HOUSTON, Long Beach. Died September 29, 1971 in Arizona, aged 58. Graduate of Temple University of School of Medicine, Philadelphia, 1940. Licensed in California in 1946. Doctor Trolinger was a member of the Los Angeles County Medical Association.

✱✱

WEBER, MANUEL L., Denver, Colorado. Died December 2, 1971 in Denver, aged 79. Graduate of the University of Moscow Faculty of Medicine, Moscow, 1919. Licensed in California in 1941. Doctor Weber was an associate member of the San Francisco Medical Society.

✱✱

WEINER, WILBUR LOUIS, Los Angeles. Died December 11, 1971 in Beverly Hills of cancer, aged 52. Graduate of the University of Arkansas School of Medicine, Little Rock, 1944. Licensed in California in 1953. Doctor Weiner was a member of the Los Angeles County Medical Association.

✱✱

WESTCOTT, ROBERT J., El Centro. Died November 26, 1971 in Calexico of cardiac arrest, aged 52. Graduate of Washington University School of Medicine, St. Louis, 1943. Licensed in California in 1951. Doctor Westcott was a member of the Imperial County Medical Society.

✱✱

WONG, OAK CHEE, Sunnyvale. Died December 5, 1971 in Santa Clara of congestive heart failure after long-term renal dialysis, aged 36. Graduate of the University of Oregon Medical School, Portland, 1962. Licensed in California in 1963. Doctor Wong was a member of the Santa Clara County Medical Society.

✱✱

WOODMAN, WILLIAM GLASS, Burbank. Died December 15, 1971 in Burbank of cancer, aged 74. Graduate of the College of Osteopathic Physicians and Surgeons, Los Angeles, 1928. Licensed in California in 1928. M.D. degree from California College of Medicine, 1962. Doctor Woodman was a member of the Los Angeles County Medical Association.

✱✱

ZUPP, LOUIS J., Tulare. Died December 4, 1971 of a massive coronary, aged 63. Graduate of Western Reserve University School of Medicine, Cleveland, 1937. Licensed in California in 1955. Doctor Zupp was a member of the Tulare County Medical Society.

Therapeutic Abortion without Inpatient Hospitalization

An Early Experience with 325 Cases

IRA M. GOLDITCH, M.D., AND JAMES E. HUSTON, M.D.,
San Francisco

■ *Analysis of 325 first trimester abortions performed on women who spent an average of less than six hours on the hospital premises, indicates that management without inpatient hospitalization is acceptable as an interim measure pending the development of alternative methods of dealing with the anticipated large number of therapeutic abortions.*

SINCE THE LIBERALIZATION of the California abortion law in 1967, requests for therapeutic abortion have increased at an astounding rate. Experience in states which liberalized their abortion laws since 1967 has been similar. In California the number of abortions has essentially doubled during each six months since the change of law, so that rates in several major hospitals have now reached 500 to 700 abortions per 1,000 births, while in at least one hospital abortions exceed births. With some 15,000 therapeutic abortions performed in 1969, it is likely that 50,000 to 100,000 abortions will have been performed in

California hospitals during 1970. Indeed, this state's Department of Health projects, on a statistical basis, that the number of requests for the procedure will continue to rise, with no plateau anticipated in the near future.

The increase in demand for abortion has usurped hospital beds, pre-empted the time of physicians, nurses and admissions personnel, and overcrowded surgical schedules, thus diminishing the time available for other elective procedures. Foreseeing no immediate relief of this acute situation, in May 1970 the Kaiser Foundation medical staff in San Francisco altered its policy to permit performance of first trimester therapeutic abortions without hospitalization. The results of our first eight months' experience are reported here.

From the Department of Obstetrics and Gynecology, The Permanente Medical Group, and Kaiser Foundation Hospital, San Francisco. Submitted April 15, 1971.

Reprint requests to: I. M. Golditch, M.D., Department of Obstetrics and Gynecology, The Permanente Medical Group, 2200 O'Farrell Street, San Francisco, Ca. 94115.

Patients and Methods

During the eight-month period May through December 1970, 353 first trimester therapeutic abortions were performed by suction curettage as outpatient procedures. The charts for 325 patients were available for review. Of this group, 149 (46 percent) were married, 158 (49 percent) were single, and 18 (5 percent) were divorced or separated. There were 234 (72 percent) white, 68 (21 percent) black and 23 (7 percent) oriental.

The age range was 14 to 35 years, with 116 teenagers and 98 women older than 30. One hundred and forty-eight (46 percent) of the women were pregnant for the first time; 47 had been pregnant at least four times previously.

Uterine size conformed to six weeks' gestation or less in 39 patients (12 percent), to eight weeks' gestation in 94 (29 percent), to ten weeks in 123 (39 percent), and at least 12 weeks in 68 (21 percent). In two cases the uterus was described as being 14 weeks', and in one as being 15 weeks' size. The uterine size at the time of curettage correlated well with assumed gestational age in 85 percent of the patients. There was a discrepancy of more than 4 weeks' gestational size in 26 patients, 14 of whose uteri were smaller than expected. Five patients were found not to be pregnant; four showed positive response to pregnancy test before curettage, while a pregnancy test was not ordered in one patient in whom a clinical diagnosis of pregnancy was based upon an enlarged uterus. In two the uterine size and secretory endometrium were normal for the nongravid state; in the other three patients, proliferative endometrium was found in normal sized uteri.

Following the necessary therapeutic abortion adjudication procedure, and in accordance with the statutory requirements of the State of California, each patient was instructed to appear in the hospital's emergency room at a scheduled time on the day before the operation, for a medical history, physical examination and laboratory evaluation. Immune globulin Rh₀ was prepared when indicated, to be given immediately after abortion. The patients were ordered to take nothing by mouth after midnight, and to appear at the admission office approximately one hour before the procedure. Patients were escorted to the surgery suite, where pre-anesthetic medication was administered. All but two were given

general anesthesia with pentothal, succinylcholine and nitrous oxide. Thirty-one patients also received methoxyflurane. One, with acute thyrotoxicosis, was given spinal anesthesia, and one patient with chronic anemia received a paracervical block. A standard vacuum aspiration apparatus* was used, followed by gentle, sharp curettage. Intravenously administered oxytocin and intramuscularly injected methylergonovine maleate were routinely used during the procedure. The patients were observed in the recovery room until fully ambulatory, then discharged home, accompanied by a relative or friend.

Results

The mean time spent on the hospital premises for the 325 patients was 5.25 hours (range: 3.5 to 8 hours). The duration of anesthesia was less than 30 minutes in 299 (92 percent) patients. The operative procedure required less than 20 minutes in 302 (93 percent) (range: 3 to 36 minutes). The estimated blood loss was less than 50 ml in 123 (38 percent) patients, 50 to 100 ml in 88 (27 percent), 100 to 150 ml in 75 (23 percent), and more than 150 ml in 39 (12 percent) patients. Two patients lost 300 ml, one lost 600 ml and one lost 1000 ml of blood. No blood replacement was required. The mean time spent in the recovery room until discharge was 3.25 hours (range: 1.5 to 5.75 hours).

Immediate postoperative complications included nausea and vomiting of a clear or yellow mucoid material by 41 patients, and moderate to heavy uterine bleeding in nine. It was necessary to admit two patients to the hospital overnight for observation because of copious bleeding. A uterine perforation occurred with a sharp curette in one patient subsequently found not to be pregnant. She remained asymptomatic and was discharged after 24 hours of observation. One patient experienced sharp pelvic pain for three hours, after which it abated. One patient aspirated vomitus during the procedure. She was treated for aspiration pneumonitis with tetracycline and steroids, and was discharged on the fourth postoperative day. Twelve of the 325 patients had delayed postabortal complications: endometritis (five cases), retained products of conception (five), subinvolution (one), and cystitis one). Curettage was repeated in all of the patients with retained products of conception.

*Berkeley Tonometer Company, Berkeley.

Two hundred and forty-eight (76 percent) patients were seen in the clinic within four weeks after abortion. All were offered some form of contraceptive. It is of interest that nine of the women frankly refused all types of contraceptive advice.

Comment

As therapeutic abortion becomes legally available throughout the nation, either by national judicial or state legislative decision, many hospitals will be confronted with an awesome increase in the number of requests for the procedure. We feel that therapeutic abortion without inpatient hospitalization is safe and efficient; and it has met with favorable patient comment.

Patient cooperation in following instructions, including preoperative restriction of oral intake, has been excellent. The addition of hydroxyzine hydrochloride (50 mg) to the preoperatively administered meperidine (50 mg) and atropine (0.4 mg), given intramuscularly, has eliminated postoperative nausea and vomiting. The use of methoxyflurane did not appear to alter blood loss or postoperative recovery time; however, the number of cases is insufficient to permit statistically significant comparison.

We have found that grasping the anterior lip of the cervix with a DeLee forceps and placing

a single-tooth tenaculum through the fenestration of the forceps affords excellent hold with minimal risk of tearing. A trial of a cervical Vibrodilator* did not facilitate cervical dilatation or shorten operating time, and its use was discontinued. The largest size Hegar dilator and aspiration tip used were found to generally correspond to the number of weeks of gestation—for example, a No. 12 Hegar dilator and an 11 to 12 mm aspiration tip would be used on a 12 weeks' sized uterus.

We agree with Margolis and Overstreet¹ that since abortion complications, if they occur, arise more than 48 hours post-abortion, the conventional 24 to 48-hour hospital stay serves no real purpose in preventing or discovering such complications. Therapeutic abortion without inpatient hospitalization has proved to be an acceptable, temporary means of accommodating the rapidly increasing number of abortion requests. It is anticipated that this system of legal abortion will ultimately prove inadequate and that more efficient alternatives, such as abortion clinics, will have to be developed.

*Berkeley Tonometer Company, Berkeley.

REFERENCE

1. Margolis AJ, Overstreet EW: Legal abortion without hospitalization (Editorial). *Obstet Gynecol* 36:479, 1970

MALE CLIMACTERIC

Once regarded as a myth, the male climacteric is now seen as a real, though rare, event. The true male climacteric is associated with failure of testicular function. A decline in androgens is measured by urinary secretion with a rise in pituitary gonadotropins. The symptoms are listlessness, loss of libido, and difficulty in concentration and recall. Occasionally there is a vasomotor crisis. If this occurs, it's almost pathognomonic. But most changes in the male at middle age are not on the basis of climacteric, but rather on the basis of psychological attitudes with symptoms expressed being manifestations of depression and anxiety. If one is not certain about the differential diagnosis between the true climacteric and the depressed middle-aged male, testosterone propionate, either intramuscularly five times a week for two weeks or in sublingual form, will result in rather rapid improvement in the individual undergoing the climacteric.

—DANIEL LIEBERMAN, M.D., Philadelphia
Extracted from *Audio-Digest Obstetrics and Gynecology*, Vol. 18, No. 6, in the Audio-Digest Foundation's subscription series of tape-recorded programs. For subscription information: 1930 Wilshire Blvd., Suite 700, Los Angeles, Ca. 90057

Maternal Mortality in California

BRUCE B. ROLF, M.D., *Los Angeles*

■ *During the period August 1957 to December 1966, the Committee on Maternal and Child Care of the California Medical Association and the State Department of Public Health studied 1,219 deaths of women who died during or within 90 days of termination of pregnancy. Twenty-two percent of the deaths reviewed were considered unavoidable. Seventy percent had one or more avoidable factors; of these, 46 percent were attributed to errors in professional judgment, and 16 percent to inadequate prenatal care by the patient herself.*

Nearly one-third (383) of the 1,219 cases reviewed were deaths from non-obstetric causes. Of the 836 deaths from obstetric causes, 260 were attributed to abortion. Preliminary figures suggest a reduction in criminal abortion deaths corresponding to the increase in therapeutic abortions since 1968.

Over one-third of the deaths occurred in Mexican and Negro mothers. Death rate for Negro was triple that for white mothers. Despite the presence of four medical schools in District II (Los Angeles County), maternal death rates were 30 to 50 percent higher than in other districts due to the large urban black and Chicano population. One rural district with a large migratory agricultural population also had high rates.

WHERE ARE THE ORPHANAGES of yesterday? Undoubtedly the chief cause for their disappearance has been the phenomenal reduction in maternal mortality during the past 50 years. A maternal death is the ultimate tragedy in present-day obstetrics.¹ In the United States no death other than homicide is studied more fully than that of a pregnant woman.²

The author is Chairman, California Medical Association Committee on Maternal and Child Care.

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Reprint requests to B. B. Rolf, M.D., 11600 Wilshire Boulevard, Los Angeles, Ca. 90025.

The first report from an American maternal mortality committee came from Philadelphia in 1931, after which local societies in other cities and then states organized committees to review maternal deaths. A statewide California program officially began August 1, 1957, jointly sponsored by the California Medical Association and the California State Department of Public Health. Effective July 1, 1970, after 13 years of such partnership, both organizations terminated financial support due to reduced budgets. At present an ad hoc committee is searching for subsidies from

local obstetrical societies and county medical societies for continuation of maternal mortality study committees within the existing framework.

Within my lifetime the maternal mortality rate has decreased progressively. Reporting of deaths in the United States began in 1915, at which time 60 white women died per 10,000 live births and 100 non-white per 10,000 live births.³ Approximately 50 years later, during the 1960's, maternal mortality rates had been reduced to 2.49 per 10,000 live births for white women and 10.13 per 10,000 for non-white women. These results can be attributed not only to improved obstetrical care, but also to advances in general medicine, nutrition and public health. However, until there is further improvement in such environmental and social problems as poor housing, malnutrition, unplanned pregnancies and inadequate total medical care, we will have more avoidable maternal deaths than occur in Sweden or our own New England States.⁴

California has a heterogenous population with so large a group of indigent or disadvantaged people that it is indeed remarkable that we have been able to reduce our maternal death rate to 2 per 10,000 live births within our present system of medical and obstetric care. Can we improve upon this in the future?

Material and Methods

For the purpose of the California study, maternal deaths include all deaths occurring during a uterine or extra-uterine pregnancy, abortion, labor, delivery or during the 90 days following termination of pregnancy. Each death is investigated by a consultant who files a special report form from which he omits the identity of the patient, the hospital and the attending physician. The case studies are then reviewed by a regional committee consisting of obstetricians, general physicians, a pathologist, an anesthesiologist and a public health physician.

The committee evaluates the cause of death, seeking to determine whether preventable factors, if any, were the responsibility of the physician, the patient or hospital facility. Results are coded by the State Health Department, after which the chairman of the California Medical Association's Committee on Maternal and Child Care may send a confidential appraisal by reg-

TABLE 1.—Maternal Deaths in California 1957-66¹³

	<i>Distribution by Race</i>	<i>Birth Rate by Race</i>
White, Mexican	17.0%	18.0%*
White, other	57.6%	60.3%
Negro	20.0%	8.3%
Indian	1.1%	0.5%
Chinese	1.3%	0.7%
Japanese	1.7%	1.2%
Other	1.2%	1.0%

*Direct information not available. Estimate based on Spanish surname indicating Mexican origin and/or parentage.

TABLE 2.—Maternal Death Rates by Race California 1930-68¹³

<i>Year</i>	<i>Total</i>	<i>White</i>	<i>Negro</i>	<i>Other</i>
1930	52.5	52.3	63.1	53.7
1935	46.7	45.9	96.2	47.9
1940	28.4	27.8	64.4	27.7
1945	16.2	15.8	—	—
1950	5.5	4.8	14.4	10.0
1955	3.7	3.2	11.6	—
1960	2.9	2.3	7.4	6.5
1965	2.9	2.5	6.7	—
1968	2.0	1.6	4.2	4.6

Rates are per 10,000 live births

istered letter to the physician or hospital according to re-identification from the case study number.

This is a report on 1219 maternal deaths studied jointly by the Committee on Maternal and Child Care of the California Medical Association and the State Department of Public Health during the period of August 1957 to December 1966. This presentation updates the seven previous reports⁵⁻¹¹ from the study committee.

Results

California holds midposition, 26th among the 50 states and District of Columbia, for report of a three-year average (1965-67) 2.62 maternal death rate per 10,000 live births.¹²

Table 1 shows that of those who have been identified at high risk over one-third are Mexican and Negro. Table 2 shows the high Negro maternal death rate has existed for many years. During the 11 years from 1958 through 1968, there was a decrease in annual live births from 348,965 to 339,221 (Table 3). This represents a decrease in birth rate from 23.7 to 17.1 (live births per 10,000 population). Maternal deaths decreased

TABLE 3.—Birth Rates and Maternal Death Rates California 1958-68¹³

	Live Births		Maternal Deaths		U.S. Maternal
	Number	Rate (x)	Number	Rate (y)	Rate (y)
1958	348,965	23.7	106	3.0	3.8
1960	371,525	23.4	107	2.7	3.7
1962	378,055	22.2	111	2.9	3.5
1964	374,441	20.5	105	2.8	3.3
1966	337,623	17.6	71	2.1	2.9
1967	336,584	17.3	95	2.8	2.8
1968	339,221	17.1	67	2.0	2.9
1969	352,937	17.3	72	2.0	na

(x) Per 1,000 population

(y) Per 10,000 live births

TABLE 4.—Maternal Death Rates for California and Maternal Mortality Study Districts, 1958-1967,¹³ by Place of Occurrence

Maternal Death Rates per 10,000 Live Births	District*					
	Statewide	I	II	III	IV	V
1958	3.0	3.3	3.2	2.9	2.4	2.6
1959	3.0	2.7	4.5	1.9	1.2	2.6
1960	2.9	1.8	3.6	2.2	3.1	4.3
1961	2.6	1.8	3.5	2.3	1.4	3.4
1962	2.9	3.1	3.6	2.1	1.7	3.9
1963	2.9	2.8	3.5	2.2	1.2	5.3
1964	2.8	2.3	3.9	2.0	2.1	2.3
1965	3.0	2.6	3.8	2.3	3.0	1.9
1966	2.0	1.7	2.8	1.7	1.1	1.5
1967	2.9	3.5	3.2	1.4	2.9	4.6
1968	2.0	1.3	2.3	1.4	3.2	2.6

* Maternal Mortality Study Districts by Geographical Area and Population, 1968

I. Southern (seven) Counties, except Los Angeles (4,422,900)

II. Los Angeles County (6,960,700)

III. Central Coast (twelve) Counties, including San Francisco Area (4,989,000)

IV. Superior (thirty) Counties, including Sacramento Valley (2,105,200)

V. West Central (seven) Counties (1,076,200)

TABLE 5.—Maternal Mortality Case Investigations Completed August 1957-December 1966 California¹⁴

Obstetric & Non-Obstetric Categories	Total	
	Number	Percent
Certified Cause of Death	1,219	100.0
Abortion	260	21.3
Sepsis	109	8.9
Hemorrhage	85	7.0
Toxemic	75	6.5
Ectopic	54	4.4
Other Obstetric Cause	249	20.4
Accident	61	5.0
Other Non-obstetric Cause	322	26.4

from 106 in 1958 (3.0 per 10,000 live births) to 67 in 1968 and 71 in 1969 (2.0 per 10,000 live births). The exception in 1967 is unexplained. Despite the presence of four medical schools in District II (Los Angeles county) maternal death rates were 30 to 50 percent higher there than other districts due to the large urban black and Chicano population (Table 4). One rural district with large migratory agricultural population also had higher rates.

The largest number (383) of 1219 cases reviewed were not "obstetrical deaths" (Table 5), due to accident or other non-obstetric cause. Abortion (260) made up the second largest group, and when combined with 54 ectopic deaths, totaled 314, pre-viable obstetric deaths. The remaining 318 patients had a likelihood of carrying a viable child. Of these nearly one-half succumbed to the "three fatal horsemen," infection, hemorrhage and toxemia, despite antibiotics, blood banks and prenatal clinics. Other obstetric causes include malpresentations, cephalopelvic disproportion, inertia, lacerations, embolism and cerebral hemorrhage during the puerperium.

Twenty-two percent of the deaths reviewed were deemed unavoidable (Table 6). Seventy percent of maternal deaths resulted from one or more avoidable factors; of these, professional judgment error occurred in 46.2 percent, inadequate care by the patient 16.2 percent, and induced abortion in 18 percent of this group. It should be noted that some cases resulted from more than one avoidable factor, so the total of the percentage incidence exceeds 100 percent. Case studies ferreted out weak spots in the care of the non-obstetric as well as the obstetric deaths.

TABLE 6.—*California Maternal Mortality Avoidable Factors, August 1957-December 1966.*¹⁴ *Obstetric and Non-Obstetric Categories**

	Number	Total Percent	Abortion	Other Obstetric	Non- Obstetric
Avoidable Factors	1,219†	100.0	260	576	383**
None	277	22.7	2	109	166
Inadequate Prenatal Care:					
Physician Only	39	3.2	—	29	10
Patient Only	198	16.2	32	112	54
Physician and Patient	38	3.1	1	24	13
Patient Error, Refusal	66	5.4	11	33	22
Induced Abortion	219	18.0	213	4	2
Judgment Error, Professional	563	46.2	74	366	123
Technical Error, Professional	93	7.6	4	68	21
Inadequate Hospital Facilities	73	6.0	8	53	12
Indeterminate	84	6.9	10	33	41

*Categories established by investigation of case

†Same case may show more than one factor

**Includes 186 cases in which pregnancy and labor were not directly responsible for death

Discussion

Results of the maternal mortality study reflect sociologic and economic as well as medical needs of the community. This study has again identified two high-risk pregnancy groups defined by race or culture. Previous reports^{7,8} also identified older mothers (age 35 or over), those of high parity (four or more children) and county hospital health care recipients as high risk groups. Reviewers often commented that a death might have been prevented had the patient had access to effective contraception. Voluntary family planning programs which are known to be the most "cost effective" way to reduce maternal deaths from unplanned pregnancies are now more readily available to the uninformed and underprivileged. Women in the high-risk category need to be reached and educated in health and family life for safer childbearing and fewer unwanted pregnancies.

Abortion deaths may become almost extinct with increased availability and acceptability of family planning and therapeutic abortion. Statistical information from this study on deaths caused by criminal abortion was presented to the state legislature before the new abortion law was passed. The new abortion law has already apparently reduced the number of women admitted to our public hospitals because of septic abortions. Inquiry was made as to whether the new

law had perceptibly affected maternal deaths in California. There was a total of only 139 deaths for 1968 and 1969 as compared with 166 for the years 1966 and 1967. Perhaps a more significant statistic is the change in maternal mortality specifically associated with abortion. I quote from a report by Dr. Edwin Jackson of the State Department of Public Health¹⁵:

"No therapeutic abortion deaths have been noted by the reporting hospitals through December 31, 1969. However, two deaths were identified in the Department's regular surveillance of maternal mortality based on death certificate review. This implies a mortality rate of 1 per 10,000 abortions, less than half the maternal mortality rate per 10,000 live births."

"There also continues to be a number of abortion deaths resulting from illegal procedures. In 1966 and 1967 combined there were 35 maternal deaths in which underlying cause of death was reported as criminal or self-induced abortion, resulting in a ratio of 0.5 deaths per 10,000 live births. There were an additional 13 deaths in which it was undetermined whether the abortion was induced or spontaneous as well as other deaths associated with criminal abortion but not reported as the underlying cause on the death certificate. Therefore, the deaths assigned to illegal abortion are understatements of the true associated mortality. In 1968 and 1969 the number of criminal (or self-induced) abortion deaths

fell to 22, a ratio of 0.3 deaths per 10,000 live births. This suggests a reduction in criminal abortion deaths corresponding to the increase in therapeutic abortions. Additional experience will be needed to confirm that this association is consistent and not the result of random variation."

Recognition that professional judgment errors accounted for the greatest number of avoidable factors has stimulated educational conferences, reports and exhibits⁵⁻¹¹ at state, county and local levels. A troubled community was benefited by our request that postgraduate training be brought to the doctors and hospital personnel by Regional Medical Planning. This project, consisting of regular visits of medical school faculty members, was continued for several months.

Inadequate prenatal care due to patient error (16.2 percent) should be an urgent concern for a society that sends extensive aid to developing countries throughout the world. The experiences of Project Hope and the Peace Corps in reaching *the people* can help us improve the lot of our own needy. The patient who neglects to seek prenatal care may have little knowledge of the health needs of pregnancy or the facilities available to her. Or she may be unable to leave her other children or job for a half day trip to a public clinic or doctor, or she may lack means or motivation to do so.

The expanding field of health care assistants will be of help in patient education as well as in patient care.

Conclusion and Recommendations

Although the maternal death rate in California has decreased to 2.0 per 10,000 live births for 1968 and 1969, one or more avoidable factors were found in more than 70 percent of the 1219

cases studied. There is room for improvement especially in the delivery of health care to the urban ghettos and to the rural migratory population. The Maternal Mortality Committee has identified the special needs of certain areas and has contributed to the continuing education of the physicians of the state.

Surveillance of maternal deaths should be continued by medical review committees of local medical societies functioning in the maternal mortality field. Legal mechanisms exist to protect confidentiality of such records.

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CANCER FELLOWSHIPS

Postgraduate Fellowships in cancer for practicing physicians are available at the University of Southern California School of Medicine and the Los Angeles County-University of Southern California Medical Center. These Fellowships are sponsored by the National Cancer Institute, are of one month's duration and carry a stipend of \$750. Separate programs are available in gynecological oncology, medical oncology, radiation therapy, tumor pathology and tumor surgery. Applicants should be Board eligible or Board certified and should submit a resumé of their professional background to Arthur J. Donovan, M.D., Program Director, Cancer Training Program, School of Medicine, University of Southern California, 2025 Zonal Avenue, Los Angeles, California 90033.

The Need for Routine Rubella Antibody Testing of Women

JAMES CHIN, M.D., ROBERT L. MAGOFFIN, M.D., AND
EDWIN H. LENNETTE, M.D., PH.D.,
Berkeley

■ *Results of rubella antibody tests performed by the California State Viral and Rickettsial Disease Laboratory on blood specimens collected in 1968 and 1969 from school children and women of childbearing age showed a slightly lower prevalence of rubella antibody in California than reported from most other areas of the United States. Among women of childbearing age, rubella hemagglutination-inhibition (HI) antibody was found in 72 percent of those tested in California compared with 80 percent to 90 percent in other areas of the country.*

Rubella antibody testing services offered by the State Virus Laboratory included situations in which a pregnant woman was exposed to a suspected case of rubella. It was shown that very few of these exposures constitute a significant risk to the fetus as most of the women already possessed antibody to rubella from past infection and in many instances the exposures were not to actual cases of rubella.

The results of this study emphasized the urgency of obtaining blood specimens from pregnant women as soon as possible after exposure to rubella or development of symptoms of rubella. The urgency and anxiety attending these situations can largely be obviated if routine rubella antibody testing of women is carried out prior to pregnancy or at the first prenatal visit.

A NATIONWIDE PROGRAM for the prevention of rubella through the routine immunization of children was started in 1969, and remains in progress. If the aim of this program is achieved, the transmission of rubella virus in the community will be

significantly reduced, thereby limiting the risk of exposure and infection of women during pregnancy. However, there is currently and there will remain, even if the spread of rubella is greatly reduced, a need to test women of childbearing age for rubella antibody levels, in order to identify those who remain at risk. The results of rubella antibody surveys performed by the Viral and Rickettsial Disease Laboratory of the

From the Infectious Disease Element, California State Department of Public Health, Berkeley.

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Reprint requests to: E. H. Lennette, M.D., Viral and Rickettsial Disease Laboratory, California State Department of Public Health, 2151 Berkeley Way, Berkeley, Ca. 94704.

California State Department of Public Health among school children and women in California provide evidence of the extent of this need and are the basis of this report.

Population and Methods

Population Groups Studied

Elementary School Children. In April and May 1969, in connection with a survey for influenza conducted by the United States Public Health Service in several cities of Southern California, capillary blood collected on filter paper discs was obtained from a total of 2,500 children 7 to 12 years of age. A representative sample of 300 specimens was tested for rubella antibodies.

Junior High and Senior High School Students. Sera collected from junior high and senior high school students were available from an influenza vaccine study conducted by the United States Public Health Service in Southern California, in October 1968. A representative sample consisting of 387 specimens was tested for rubella antibody.

Women Employees of Hospitals and Medical Laboratories in the San Francisco Bay Area. Because of the potentially huge volume of tests, the Virus Laboratory was unable to provide routine testing in anticipation of pregnancy or administration of rubella vaccine for the entire female population. However, when not available locally, rubella tests to determine immune status were provided for female personnel of hospitals and medical laboratories who are potentially at high risk of exposure in their employment. During 1969 tests were performed on 275 women in medically-related occupations in California.

Pregnant Women. Serologic tests for the diagnosis of rubella were routinely offered to confirm or rule out rubella in patients with exanthems or other suspicious clinical signs of rubella and to assess the immunity status of pregnant women exposed to rubella or rubella-like disease. For diagnosis of suspected clinical cases, acute- (within a week of onset) and convalescent- (two to three weeks after onset) phase blood specimens were requested. In cases of *exposure only* a single blood specimen was requested as soon as possible after exposure. Only those pregnant women who had a blood specimen collected within two weeks of exposure were included in this study. A second blood specimen was fre-

quently submitted from those women whose initial blood specimen had no demonstrable rubella antibody. The results of tests performed during 1969 were utilized for this study.

Laboratory Methods

All of the rubella hemagglutination-inhibition (HI) tests were performed in the Viral and Rickettsial Disease Laboratory. The preparation of the hemagglutinating antigen and the test method used in these studies have been described elsewhere.¹ Sera were examined for rubella HI antibody at dilutions of 1:8 through 1:1024 against 4 units of antigen. Methods for the preparation and testing of eluates from filter-paper discs used in collection of finger-prick blood samples have been previously reported.² Comparative studies in this laboratory, using serum (from venipuncture) and capillary blood collected on filter paper discs from the same individuals, showed that similar rubella HI antibody titers were obtained with both types of specimens. Monto et al³ also found comparable antibody titers in an evaluation of the use of both types of blood specimens for rubella HI tests.

Results

The prevalence of HI antibody to rubella in primary and secondary school age children and women employees of hospitals and laboratories is presented in Table 1. A steadily increasing prevalence is noted with age. The sharpest increase is observed in the elementary school age group between the ages of 7 and 12 and by the time young women reach the childbearing age more than 60 percent have evidence of past infection with rubella virus.

Table 2 presents the prevalence of rubella antibody found in pregnant women comparing those who were only exposed to a suspected case of rubella and those who showed clinical symptoms (usually a febrile exanthem) suggestive of rubella. The latter group is subdivided to show results on serum specimens obtained within one week or more than one week of onset. The age distribution of pregnant women exposed to rubella and the female hospital employees was essentially similar, whereas the group with clinical symptoms was comprised of slightly younger women. Most of the pregnant women (approximately 70 percent) were observed during the first trimester of pregnancy.

**TABLE 1.—Prevalence of Hemagglutination-Inhibition Antibody to Rubella Virus
In Selected Population Groups—California, 1968-1969**

Population Group	Elementary School Children			Jr. and Sr. High School Children				Women Hospital Personnel		
Age Group, Years	7-8	9-10	11-12	12-13	14-15	16-17	15-24	25-34	≥35	Unknown
Number Tested	100	100	100	199	88	100	104	97	16	58
Percent with Titer ≥1:8	28.0	45.0	46.0	53.3	62.5	62.0	71.2	71.1	81.3	74.1
Percent of Total Group with Titer ≥1:8	39.7			57.6				72.4		

**TABLE 2.—Prevalence of Hemagglutination-Inhibition Antibody to Rubella Virus
In Pregnant Women Exposed to Rubella-like Illness or with Symptoms of Rubella—
California, 1969**

Population Group	Pregnant Women Exposed to Rubella or Rubella-like Illness Sera collected within two weeks of exposure				Pregnant Women with Clinical Symptoms of Rubella Sera collected within one week of onset				Pregnant Women with Clinical Symptoms of Rubella Sera collected after one week of onset			
	15-24	25-34	≥35	Unknown	15-24	25-34	≥35	Unknown	15-24	25-34	≥35	Unknown
Age in Years	15-24	25-34	≥35	Unknown	15-24	25-34	≥35	Unknown	15-24	25-34	≥35	Unknown
Numbers Tested	152	243	19	57	29	22	0	5	17	9	2	6
Percent with Titer ≥1:8	74.3	71.2	78.9	77.2	44.8	36.4	—	20.0	76.5	100.0	100.0	100.0
Percent of Total Group with Titer ≥1:8	73.2%				39.3%				88.2%			

The prevalence of preexisting HI antibody in sera of pregnant women obtained within two weeks of exposure to a rubella-like disease (73 percent) was almost identical to that found in the survey of female medical personnel (72 percent). Among the 90 pregnant women with clinical symptoms of rubella, antibody was found in 22 of 56 (39 percent) of the acute-phase serum specimens collected within a week of onset, and in 30 of 34 (88 percent) initial specimens collected more than a week after onset. Thus, in those with clinical signs of rubella, the prevalence of antibody in early acute-phase specimens was far lower and in later specimens appreciably higher than that observed in the other groups of women whose antibody was unrelated to a clinical episode.

Of the pregnant women without demonstrable rubella antibodies in the initial blood specimen, second blood specimens were obtained from 48 of the 126 with exposure only and 37 of 38 in the group with clinical symptoms. The HI antibody titers of the second specimens (collected in most cases from one to three weeks after the first specimen) are presented in Table 3. Among 48 women with a history of exposure only, two subsequently showed HI antibody titers of 1:32 or

greater; of the 37 clinically suspect women initially seronegative, 27 developed antibody with titers ranging from 1:32 to 1:1024 or greater.

Discussion

Substantial differences in the prevalence of antibody to rubella have been observed in different geographic areas.⁴ The groups surveyed in this study were selected and thus are not necessarily representative of the total population in California. The results of our survey show a somewhat lower prevalence of rubella antibody by age compared with those published for similar population groups in most other areas in the continental United States. Severs et al⁵ similarly found a lower prevalence of rubella antibody in a group of pregnant women from Los Angeles compared with groups from Memphis and Baltimore in 1969. The reasons for this apparently lower incidence of rubella on the West Coast are unknown. Peak years of rubella in California have generally coincided with those recorded nationwide.⁶ The last large outbreak of rubella in the United States, which was first noted on the East Coast in the spring of 1964, was not experienced in California until early 1965. Although

TABLE 3.—Rubella Antibody Titers of Follow-up Sera from Pregnant Women Who Were Initially Seronegative (less than 1:8)

<i>Antibody Titer of Second Blood</i>	<i>Number of Women with Exposure Only</i>	<i>Number of Women with Clinical Symptoms</i>
Total	48	37
<8	44	10
8	1	
16	1	
32		2
64	1	1
128	1	5
256		7
512		8
≥1024		4

this epidemic was somewhat delayed, its impact was as severe as that observed in other areas of the country.⁷

For serologic tests to be useful for supporting clinical judgments concerned with suspected rubella or exposure to it, the time at which the specimens are collected is of critical importance. When a pregnant patient presents with a history of exposure to a possible case of rubella and a specimen obtained promptly (within 14 days of initial contact) shows the presence of antibody, one may conclude that the patient had experienced infection in the past and was immune at the time of exposure. Additional follow-up specimens in these instances are not usually needed nor helpful. If, however, the blood specimen is collected more than 14 days after exposure, interpretation becomes highly uncertain since by that time it cannot be clearly determined whether antibody, if present, was already present at the time of exposure or stems from a current subclinical infection. The same critical timing of the collection of blood specimens applies to those situations in which the patient presents with symptoms suggestive of rubella.

The prevalence of antibody to rubella in the groups of women with rubella-like disease observed in our study illustrates the importance of this point. Fewer than 40 percent of women who had an acute-phase blood specimen collected within a week of onset had demonstrable antibodies to rubella. The relatively low level of immunity in this group reflects in part the younger age of this group compared to the other survey groups of women, but also undoubtedly

reflects the clinical selection of susceptible women (that is, without antibodies to rubella) who were having a primary clinical infection with the rubella virus. The low frequency of rubella antibody in sera collected within the week of onset contrasts with the high frequency (88 percent) of antibody in initial blood specimens drawn more than a week after onset of symptoms. Clearly, many of the illnesses in question were in fact rubella, but because of the delay in obtaining a blood specimen definitive laboratory diagnosis in the individual cases could not be made. The need for physicians and patients to recognize rubella exposures and rubella-like illnesses as early as possible so that laboratory studies can be carried out without delay was also emphasized by a recent British study on rubella serologic tests during pregnancy.⁸

Previous recommendations⁹ have called attention to the use of rubella tests as a routine procedure for determining immunity status of women at the time of the first prenatal examination, or preferably before they become pregnant (premarital examination or in family planning clinics). The results presented here clearly point up the need for rubella antibody testing of women as a routine practice. The largest number of requests for diagnostic tests for rubella by the Virus Laboratory stemmed from situations in which a pregnant woman was exposed to suspected cases of rubella. These situations almost invariably produced a great deal of anxiety for the patient and her family and an added concern for the physician, and often developed into minor "crises" with regard to the urgent obtaining of blood specimens for testing, awaiting results and then interpreting the findings when received. Our study showed that very few of these exposures entailed a significant risk to the patient because most women already possessed antibody to rubella from past infection, and many of the exposures were not to actual cases of rubella. These findings, however, are of little assurance to the patient or of practical use to the physician in evaluating the individual case at the time of exposure to a rubella-like disease when her antibody status is unknown. These all-too-frequent episodes can be prevented if routine rubella antibody testing of women is carried out before pregnancy or at the time of the first prenatal visit along the same lines as routine tests for syphilis and Rh typing.

Those women found by serologic testing to be susceptible to rubella (that is, lacking antibody) can be considered for rubella immunization provided precautions are followed to assure that the patient is not pregnant at the time of immunization and conception is avoided for at least two months after immunization.¹⁰ If rubella antibody screening is not performed until pregnancy occurs, the result of the serologic test is still of paramount importance for the management of the pregnancy. Those women with antibodies can be reassured if they are subsequently exposed to a rubella-like disease during pregnancy. In those without demonstrable antibody the physician is alerted to the patient's susceptibility, can caution the patient of this, observe closely for clinical signs of rubella, and follow up with additional antibody tests should exposure or clinical signs occur. In addition, all rubella susceptible pregnant women can be considered candidates for rubella immunization in the immediate postpartum period.¹¹

Even when rubella is effectively controlled, many pregnant women will continue to be exposed to rubella-like rashes. A record of a rubella antibody test at the outset of pregnancy will thus still be necessary in such situations. Routine tests will also be of great value in the

continuing assessment of the susceptibility of this population. Rubella antibody tests are now widely available from clinical and local public health laboratories in California and should be routinely performed in women as an integral part of the current effort to control rubella.

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BED-WETTING AN ALLERGIC REACTION?

There is a belief that if a child wets the bed, he may need an allergist rather than a psychiatrist. The cause could be allergy. Recently a study on 100 chronic bed-wetters between the ages of four and 12, all of whom had no apparent organic disorder, disclosed that 87 had ceased to wet the bed within five days as long as they avoided their particular food allergens. The food most commonly found to be at fault was cow's milk. With a history of allergy in the family and if the bed-wetter exhibits other allergic symptoms such as chronically stuffy nose, constant tiredness, or classical skin rashes, it is quite probable that the bed-wetting is due to food allergy. A diet excluding milk, chocolate, eggs, chicken, wheat, corn, citrus fruits, tomato, pork, and onion should stop the bed-wetting within five days in about 90 percent of the cases according to recent reports. After the bed-wetting is controlled, those foods are reintroduced so that the child is not on an elimination diet too long.

—ARTHUR J. HORESH, M.D., Cleveland
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Unusual Dermatoglyphic Findings Associated With Cytomegalic Inclusion Disease of Infancy

A First Report and Practical Review

HARRY T. WRIGHT, JR., M.D., AND CHARLES E. PARKER, M.D., *Los Angeles*, AND
JAMSHED MAVALWALA, PH.D., *Toronto*

■ *Infection with the human cytomegalovirus has a teratogenic effect on the fetus during the first trimester of gestation as does rubella. Since unusual dermatoglyphic findings have been observed in infants with congenital rubella infection, the present study was designed to determine whether or not unusual dermatoglyphics occur in patients with cytomegalic inclusion disease of infancy. Analysis of dermatoglyphics in 15 infants with cytomegalic inclusion disease revealed unusual features in all infants. These features are reported here for the first time and are compared with dermatoglyphic findings in a normal population as well as with those of available parents of the infants.*

DERMATOGLYPHICS, literally "skin carvings," is the term given to the configurations formed by the furrows and epidermal ridges in the skin of the digital tips, palms and soles of all primates.¹ Cummins and Midlo's comprehensive treatise on the significance, description, methods and biologic aspects of dermatoglyphics is used as the basis for modern studies.² By the sixteenth week of gestation the epidermal ridges are well developed, but the process is probably not complete before 24 weeks.³ Once complete, the epidermal

ridges remain unchanged for life, except for growth in size. Hence the patterns which remain stable and characterize an individual are present at birth.³

Unusual dermatoglyphics were first observed in patients with Down's syndrome by Cummins.⁴ In 1966, Alter summarized the unusual dermatoglyphics observed in 68 clinical disorders including not only chromosomal aberrations and single gene disorders but also diseases of uncertain genetic transmission, such as congenital heart disease and psoriasis, and diseases due to toxic or environmental factors, such as thalidomide and rubella.³

Like rubella, the cytomegalovirus has a teratogenic effect during the first trimester of gestation and one might speculate that alterations in der-

From the Department of Pediatrics, University of Southern California School of Medicine; the Childrens Hospital of Los Angeles; and the Department of Anthropology, University of Toronto, Canada.

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Reprint requests to: H. T. Wright, Jr., M.D., Childrens Hospital of Los Angeles, P.O. Box 54700, Terminal Annex, Los Angeles, Ca. 90054.

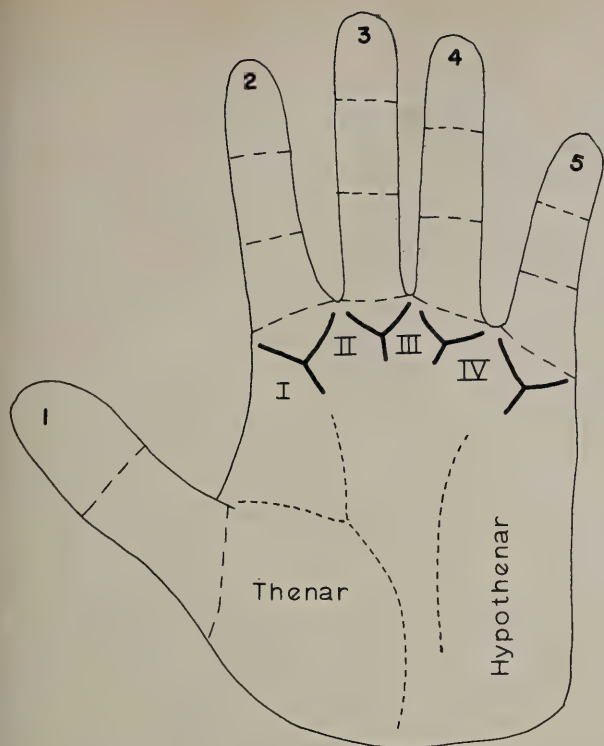


Figure 1.—Areas of the hand having dermatoglyphic patterns.

matoglyphics would be present in infants with cytomegalic inclusion disease since alterations occur in infants with congenital rubella infection.^{5,6}

Analysis of dermatoglyphics in 15 infants with cytomegalic inclusion disease of infancy revealed unusual features in all 15. These features are reported here for the first time and are compared with dermatoglyphic findings in a normal population as well as with those of available parents.

Methods

Dermatoglyphics can be cleanly and permanently recorded by several techniques.³ In the present study dermatoglyphic prints were obtained by use of inkless kits supplied by Faurot and Hollister. The advantages of the inkless methods are tidiness and relative cleanliness for the subject tested. The digits, palms and soles were covered with the appropriate fluid and then an impression was made on special sensitized paper. Prints on some patients were obtained by the photographic method utilizing an optical means of enhancing the contrast of surface reliefs as described by Harrick.⁷

The normal hand has 11 significant areas where sulci, or furrows, and ridges form distinct pat-

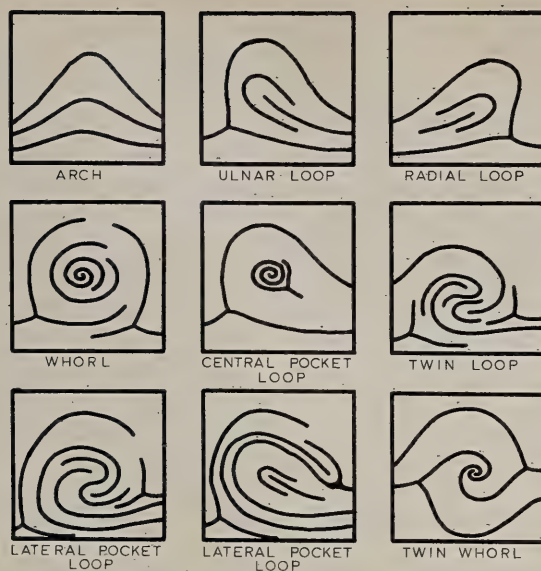


Figure 2.—Illustration of various dermatoglyphic digital patterns.

terns (Figure 1). The areas are the five tips of the fingers, the four interdigital areas, the thenar eminence and the hypothenar eminence of the palm. Usually flexion crease lines are discussed with dermatoglyphics, although they are quite different in origin.

Subjects

Since 1960, 30 infants with cytomegalic inclusion disease have been studied at the Childrens Hospital of Los Angeles to determine clinical manifestations and sequelae of this disease. Fifteen of these patients have been admitted to the Clinical Research Center on one or more occasions for extensive studies to determine the long-term effects of a transplacental viral infection.

In all cases, the diagnosis was based on the presence of clinical manifestations of the disease as well as the repeated isolation of human cytomegalovirus from urine specimens and throat swabbings. This virus was identified by the classical cytopathic effect observed when specimens were inoculated into human fetal fibroblasts, and by subsequent cytochemical studies which demonstrated appropriate intranuclear and cytoplasmic inclusion bodies.⁸

In the present study dermatoglyphics on the patients are compared with those of their parents, or frequencies are quoted from large studies from Europe, since the patients are primarily of European descent.

TABLE 1.—*Digital Dermatoglyphic Patterns of 15 Patients with Cytomegalic Inclusion Disease*

	Right Hand					Left Hand					Total Ridge Count
	1	2	3	4	5	1	2	3	4	5	
B.B.	+	+	-	+	+	+	+	+	+	+	151
P.C.	+	-	-	-	-	+	-	-	-	-	68
W.E.	+	+	+	+	+	-	+	+	+	-	162
B.K.	-	-	-	-	-	-	-	-	-	-	0
J.M.	-	+	-	+	+	-	+	+	+	-	170
D.M.	+	+	+	+	-	+	+	+	+	-	208
D.P.	-	+	+	+	-	-	-	+	+	-	162
G.R.	+	+	-	+	-	+	-	-	-	-	192
E.S.	+	-	-	-	-	+	-	-	-	-	73
J.A.	-	-	-	-	-	-	-	-	+	+	76
E.M.	+	+	+	+	+	+	+	+	+	+	198
T.P.	-	-	-	-	-	-	-	-	-	-	not available low
M.R.	-	-	-	+	-	-	-	-	-	-	56
D.G.	-	-	-	-	+	-	-	+	+	-	196
J.J.	-	+	-	+	+	-	+	-	+	-	not available medium

- Arches and Loops
+ Whorls and Complex Patterns

Definitions and Results

Fingers

Tips. The skin ridges on the fingers form various patterns ranging from the geometrically simple arch to loops and to more complex patterns such as whorls, central pocket loops, twin loops, lateral pocket loops and twin whorls (Figure 2). In Scotland Yard data³ on 5,000 normal individuals, the incidence of complex patterns on the fingers was 25 percent, whereas the general trend observed in our patients was an increase of complex patterns to 43 percent. Two of our patients, B.K. and T.P., had extremely simple patterns on all ten fingers (Table 1). They most probably inherited their remarkably high frequency of arches. Analysis of the dermatoglyphics of B.K.'s parents, necessary for comparison, is not obtainable; however, analysis of the dermatoglyphics of T.P.'s parents confirms this assumption, since they have a high frequency of simple patterns (Table 2).

Usually, certain fingers will more frequently show complex patterns than other fingers.² In our patients, it would appear that the distribution of the complex patterns on individual fingers was different from that normally expected. For example, the fourth and fifth digits on each hand ordinarily have smaller and less complex patterns; however, among our patients this trend

TABLE 2.—*Digital Patterns of Parents of Children with Cytomegalic Inclusion Disease*

	Right Hand					Left Hand					Total Ridge Count
	1	2	3	4	5	1	2	3	4	5	
<i>Mother</i>											
D.M.	-	-	-	+	-	+	+	-	+	-	162
G.R.	+	-	-	-	-	+	-	-	-	-	196
E.S.	-	-	-	-	-	-	-	-	-	-	21
J.A.	-	-	-	-	+	-	-	-	-	+	49
E.M.	+	+	+	+	+	+	+	+	+	+	169
T.P.	-	-	-	-	-	-	-	-	-	-	70
D.G.	-	-	-	-	-	-	-	-	-	-	128
J.J.	+	+	-	-	-	-	-	-	-	-	149
<i>Father</i>											
E.S.	+	-	+	+	-	+	-	-	-	-	178
J.A.	+	+	+	+	+	+	+	+	+	+	190
E.M.	+	-	-	+	+	+	+	-	+	+	181
T.P.	-	-	-	+	-	+	-	-	-	-	112
D.G.	+	+	+	+	+	+	+	+	+	+	226

- Arches and Loops
+ Whorls and Complex Patterns

was not observed and complex patterns frequently were present on the fourth digit (Table 1).

Ridge Count. The ridge count of each finger is obtained by counting the number of ridges that lie between a point on the outer edge of the pattern, the triradius (designated "y" in Figure 3), and a central, or core, ridge of the pattern (designated "x" in Figure 3). The total count is obtained by adding together the higher ridge count from each of the ten fingers. Holt⁹ has reported an average total ridge count of 145 in a study of 825 British males. The average total ridge count of the nine males in the present series (B.B., W.E., J.M., D.M., D.P., G.R., E.S., J.A. and E.M.) on whom a total ridge count could be made was 155.

Palms

Flexion Creases. Usually flexion crease lines are discussed with dermatoglyphics although anatomically they are quite different in origin (Figure 4). These are large deep grooves which generally overlie the flexural aspect of joints of the fingers and the rest of the hand. Two distinct, comparatively long, transverse flexion creases overlie the metacarpophalangeal joint (Figure 4, lines 1 and 2). When the two creases are fused into a single horizontal fold, they are referred to as a simian line. This occurs with high frequency in Down's syndrome.¹⁰ Transitional forms occur when two creases are joined

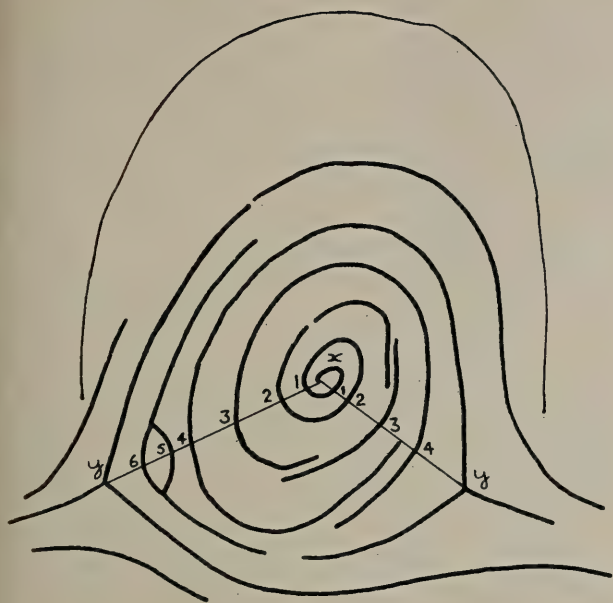


Figure 3.—Method of dermatoglyphic ridge counting.

by a bridge. Although transitional transverse flexion creases occasionally occur in the normal population, they were observed on both hands of eight of our patients and another patient had a classical simian line on one hand.

Triradii. Another important element of patterns on the palm is the triradius, which is a Y-shaped junction where three ridges, sometimes referred to as radiants, meet. The normal hand has at least five triradii which are dermatoglyphic landmarks (Figure 5). Four are located at the base of the index, middle, ring and fifth fingers and are termed *a*, *b*, *c*, and *d*. At least one medial triradius is present on the palm between the hypothenar and thenar areas. The proximal medial triradius (pmt), termed *t* and commonly called the axial triradius, occurs normally close to the carpal creases. However, other distal medial triradii (dmt) may be present, invariably associated with patterns on the hypothenar area. Such distal medial triradii, termed *t'* and *t''*, must not be confused with an elevated proximal medial triradius which occurs when no triradius is present near the carpal creases. Proximal medial triradii were not elevated in our patients, but distal medial triradii occurred in association with hypothenar patterns.

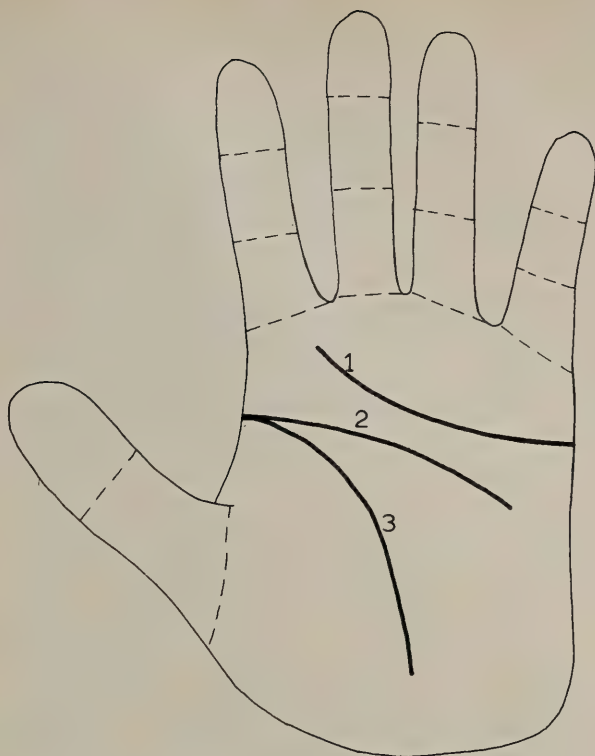


Figure 4.—Position of palmar flexion creases.

a-b ridge count. One measure of ridge breadth on the palm is obtained by counting the number of ridges that are cut by a line drawn between triradii *a* and *b* (Figure 5). Counting both hands, Fang¹¹ reported a mean a-b ridge count of 85 in a normal Ontario population of British extraction and a mean total ridge count of 84 in a study of normal British students. The mean total a-b ridge count on our patients was 80.

Main Lines. The proximal ridge radiant that emerges from each of the triradii *a*, *b*, *c*, and *d* is termed a main line. The four main lines usually cross the palm in a transverse fashion except for line *A*, which frequently is longitudinal. In our patients all main lines tended to be transverse, as in Figure 5.

Palmar Patterns. As far as the hypothenar area is concerned, Cummins and Midlo² found that 34.3 percent of 1,281 normal German males had patterns of varying complexity on the hypothenar area. Seven of our 15 patients (46.7 percent) had complex hypothenar patterns on both palms, and another had a complex pattern on the right palm only (Table 3). This suggests an increased frequency of complex hypothenar patterns among these patients.

In a normal population, the thenar-first inter-

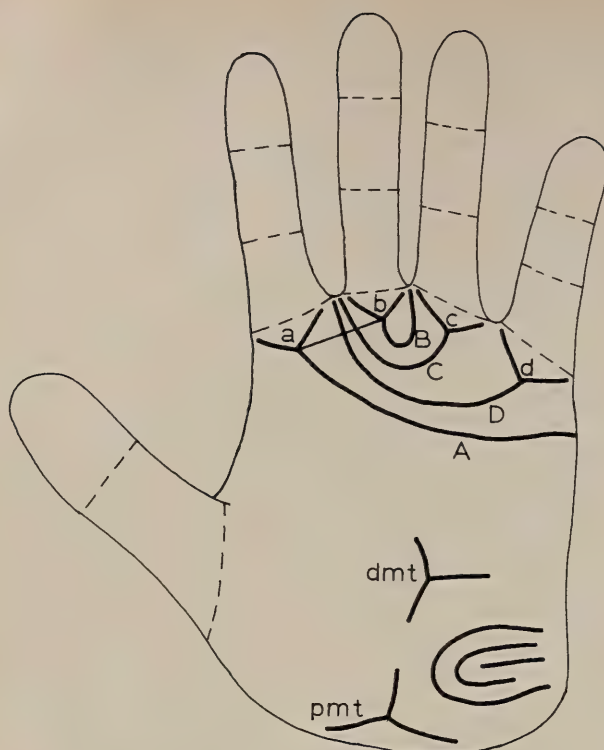


Figure 5.—Position of various triradii of the hand.

digital area is usually patternless. The frequency of patterns in interdigital area II was found to be 11.8 percent by Cummins and Midlo,² and the frequency of patterns in interdigital areas III and IV was 53.6 percent and 60.5 percent, respectively. In our patients, the thenar-first interdigital area was patternless except for the left palms of two patients; one patient had an interdigital area II pattern on the right palm and another had an interdigital area II pattern on both palms. The frequency of interdigital areas III and IV patterns among our patients was 53.3 percent (16 of 30) and 77 percent (23 of 30), respectively, suggesting an increase in frequency from the normal in the fourth interdigital area (Table 3).

Soles

Sole prints were obtained for ten patients. All of them had patterns in the hallucal area of both feet, except one patient who had an arch tibial on the left sole. Of the 19 hallucal patterns observed, five were complex patterns such as spiral whorls or lateral pocket loops, suggesting an increased frequency of complex patterns. The remainder were all distal loops. Very few studies are available on dermatoglyphics of soles and further analysis is necessary.

TABLE 3.—Interdigital Palmar Patterns of Patients

	Hypo- thenar	Tb/I	II	III	IV	a-b ridge count
	R L	R L	R L	R L	R L	
B.B.	+ +	- -	- -	+ +	+ +	80
P.C.	+ +	- +	- -	+ +	+ +	82
W.E.	+ +	- -	- -	+ +	+ +	85
B.K.	+ +	- -	- -	+ +	- +	81
J.M.	+ +	- -	- -	- -	+ +	79
D.M.	+ +	- -	- -	+ -	- +	75
D.P.	- -	- -	+ -	- -	- +	65
G.R.	- -	- -	- -	- -	+ +	89
E.S.	+ -	- -	- -	- -	+ +	86
J.A.	- -	- -	+ +	+ +	+ +	46
E.M.	- -	- -	- -	+ -	- +	73
T.P.	+ +	- -	- -	+ +	+ +	76
M.R.	- -	- -	- -	+ -	- -	93
D.G.	- -	- -	- -	- -	+ +	113
J.J.	- -	- +	- -	+ -	- +	74

R Right Hand
L Left Hand
+ Present
- Absent

Dermatoglyphics on Parents

Dermatoglyphics were performed on parents of eight of the 15 children. Prints were obtained from eight mothers and five fathers. Comparative data on the parents is tabulated in Tables 2 and 4. It is of interest to note that in the case of the three patients, E.S., J.A., and T.P., all of whom had a low incidence of complex patterns and a concomitant low total ridge count, it was the mothers who also showed a low frequency of complex patterns and a low total ridge count. All three fathers had complex patterns and high total ridge counts.

While two of eight mothers (D.M. and E.M.) had complex patterns on the fourth digit of both hands, three of five fathers had complex patterns on the fourth digit of both hands and the other two fathers had this feature on the right hand only. Eleven of 15 patients tested had this trait on one or both hands.

A single transverse flexion crease was present on the right hand of the mother of D.G. only. Fifteen percent (4 of 26) of the palms of the parents had a transitional transverse flexion crease, whereas 53 percent (16 of 30) of the palms of the patients had transverse flexion creases.

Except for line A, the main lines on all the parents were transversely oriented. All main lines were transversely oriented in the children.

TABLE 4.—Interdigital Palmar Patterns of Parents

	Hypo- thenar		Tb/I		II		III		IV		a-b ridge count
	R	L	R	L	R	L	R	L	R	L	
<i>Mother</i>											
D.M.	—	—	—	—	—	—	—	—	—	+	65
G.R.	—	—	—	—	—	—	—	—	+	+	117
E.S.	—	+	—	—	—	—	—	—	+	+	83
J.A.	—	—	—	—	+	—	—	+	+	+	74
E.M.	—	—	—	+	—	—	—	—	+	+	94
T.P.	—	—	—	—	—	—	+	+	—	—	92
D.G.	—	—	—	—	—	—	—	—	+	+	112
J.J.	—	—	—	—	—	—	+	+	+	+	79
<i>Father</i>											
E.S.	—	—	—	+	—	—	+	—	—	+	90
J.A.	—	—	—	—	—	—	+	+	+	+	91
E.M.	—	—	—	+	—	—	+	—	—	+	76
T.P.	—	—	+	+	—	—	+	+	—	—	illegible
D.G.	—	—	—	—	—	—	+	—	—	+	80
R Right Hand											
L Left Hand											
+ Present											
— Absent											

Whereas 30 percent (3 of 10) of the palms of male children whose fathers were examined had hypothenar patterns, none of their fathers had this trait. Forty-five percent (9 of 20) of the palms of the male children in the study had hypothenar patterns.

Sole prints were available on four parents, and only the father of T.P. had complex hallucal patterns on both soles. The mother of T.P. had a complex hallucal pattern on the right sole. The other patterns were all loops or arches. Whereas, as was previously mentioned, all the ten infants tested had patterns in the hallucal area (except for one foot on one patient), only one of the four parents tested had patterns in the hallucal area of both soles.

Comment

Achs and associates⁷ pointed out that children with major congenital malformations have unusual dermatoglyphic markings, most frequently represented by simian lines, bilateral distal axial triradii, single flexion creases and radial loops on other than the second digit.

Stough and Seely¹² suggested that 40 to 50 percent of infants with congenital rubella have unusual dermatoglyphic findings including simian lines, distal axial triradii, radial loops other than on digit 2, complex patterns on the digits

and an increase in patterns in the third interdigital area.

Since these findings also occur in various syndromes, such as mongolism, D trisomy, 18 trisomy and rubella, they have been considered non-specific indicators of altered embryonic development and not specific for a given syndrome.⁷

Because cytomegalic inclusion disease of infancy, like rubella, is associated with major abnormalities, such as microcephaly, hearing loss, prematurity and growth retardation, this study was planned to investigate the presence of unusual dermatoglyphic findings in children with this disease.

As expected, unusual dermatoglyphic findings were found and it is believed most likely that they indicate abnormal influences in early gestation.

As far as controls are concerned, it is inappropriate to match controls for age and sex. Age does not matter because once dermatoglyphics are formed they do not change except for size; and there is a low bisexual variation. The frequency in patterns in one population changes from gene pool to gene pool. Appropriate controls are parents, siblings and relatives. It is also considered appropriate to use what is considered "normal" frequencies from large samples within the genetic population.

Until recently, it was generally agreed that ridge counts, patterns and flexion creases were primarily under genetic control. Mulvihill and Smith¹³ speculated that dermatoglyphics are a direct consequence of the surface topography of the fetal hand during the period of dermal ridge development.

Attempts were made to apply statistical methods to the results obtained in this study. No significance was demonstrated. Unfortunately, extremely small numbers were available for evaluation but we speculate that if the trend continues with larger numbers, results would most likely acquire significance.

The present study supports the concept that environmental teratogens such as the cytomegalovirus may significantly alter dermatoglyphics, and it also supports the suggestion that dermatoglyphics may serve as a marker of a deleterious intra-uterine experience during early gestation.

Summary

This investigation of the dermatoglyphics in children with cytomegalic inclusion disease indicates that such children have: (1) a high frequency of complex patterns on the fingers, (2) a high frequency of transitional transverse flexion creases, (3) transversely oriented palmar main lines, (4) a high frequency of complex hypothenar patterns with distal medial triradii, (5) a high frequency of patterns in interdigital areas III and IV, and (6) a high frequency of complex hallucal patterns on the soles.

Since these findings occur in other syndromes and in children with major malformations, they most likely indicate an unusual influence in early gestation and are not diagnostic for any one disease.

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CORONARY CARE UNITS' EFFECT ON MORTALITY

Can we demonstrate that the introduction of specialized coronary care units does reduce mortality from acute myocardial infarction?

The answer is yes. There has not been a decisive study to indicate the value of coronary care. However, in several cities of the world, Melbourne, Australia, Toronto, Canada, New York City, and Philadelphia, people were admitted to coronary care units on the basis of bed availability. Some went to general care; some went to coronary care. Nobody made decisions. When you examine the statistics from the hospitals involved, there is an advantage to coronary care as against ordinary care, a reduction in mortality of about 30 percent. That is, mortality drops from 30 percent to 20 percent.

Would you like to put those figures into context? How many people get to the point where they could enter a coronary care unit?

The percentage of people dying before they can be admitted to a coronary care unit has consistently been about 60 percent. Sixty to 70 percent of patients die outside the purview of the hospital. Then taking the survivors, 30 percent of those who are not put into a coronary care unit will succumb while 20 percent of those reaching so-called "ideal" facilities will die. That's not 20 percent of the total population; that's 20 percent of those reaching this special environment.

—DISCUSSION ON NEW TRENDS IN TREATING ACUTE MYOCARDIAL INFARCTION

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Counseling Parents of Retarded Children

MARIO VALENTE, M.D., Los Angeles

■ *Recently pediatricians have become more interested in the retarded child and his family and have come to realize that they have been ill-prepared to face the many problems that continually arise. A basic understanding of the role of parents and their aspirations, coupled with a knowledge of interviewing techniques will enable them to face these problems with greater assurance. In addition, a knowledge of the community facilities and resources is necessary. This will entail direct contact with schools, parent groups, state hospitals for the retarded as well as state and local agencies which deal with the retarded.*

ONE OF THE MOST DIFFICULT tasks facing a pediatrician is that of counseling the parents of a retarded child. It is far more painful than counseling the parents of a dying child, for death is irrevocable and final and its wounds will often be healed with time. The diagnosis of mental retardation, on the other hand, often brings with it the specter of chronic sorrow for the parents and a life of disability for the child.

How the pediatrician handles this situation depends upon his experiences in such matters, his understanding of the factors underlying parental feelings and the manner in which they are expressed, and all too often his own personal feelings. Rarely will his training either in medical school or residency have prepared him for the task.

The pediatrician has an important role in the diagnosis and management of retarded children and in the more difficult task of helping parents live with this problem so that they can cope with the crises as they arise during the various stages of development of their retarded child.^{1,2}

The two medical specialties most involved in the field of mental retardation, pediatrics and psychiatry, view the problem from different perspectives. By training, the pediatrician considers mainly the organic and developmental factors, the psychiatrist mainly the psychosocial. The pediatrician, trained mainly to treat acute conditions, usually has little interest in the care and management of the retarded child with all the attendant chronic, often unsolvable problems. The psychiatrist, on the other hand, tends to rely too heavily on his training in psychodynamic theory and practice. What is most needed is a happy synthesis of these two approaches in a physician who is not only well trained in the organic aspects of mental retardation but who also has an understanding of the emotional impact of this condition on both the child and his family.

Training programs in both psychiatry and pediatrics are now trying for this synthesis, but in the meantime most practicing pediatricians and psychiatrists have not had the benefit of this new training philosophy.

This paper is based upon ten years' experience by the author in the field of mental retardation,

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Reprint requests to: M. Valente, M.D., Neuropsychiatric Institute, University of California, Los Angeles, 760 Westwood Plaza, Los Angeles, Ca. 90024.

first in a state institution and more recently in a university affiliated teaching and research center for the mentally retarded. An attempt will be made to outline some general principles for practicing pediatricians. It should be borne in mind, however, that each family unit differs from the next and that its manner of handling this problem depends upon such factors as the stability of the marriage, family ties, religious attitudes, economic status, education, environment and, last but not least, sociocultural factors.^{3,4}

Before a pediatrician can discuss the diagnosis and management of a retarded child with the parents, it is important that he reflect upon the hopes and aspirations all parents have for their children.⁵ All parents hope that their children will accomplish much more than they as adults were able to accomplish. One can then imagine the shock upon realization that this dream will not come true. Feelings of guilt, shame and despair will arise and the parents will begin to ask questions such as "Why did it happen to me?", and "What did I do wrong?", and they will very often initially blame themselves.^{6,7} With time, they will begin to recover from this initial shock and then will begin to ask questions such as "Why?", "Will it happen again?" and, ultimately, the most important of all, "What can be done for my child?" These last three are fundamental questions which a physician must answer over a period of time.

Sometimes the pediatrician will face extreme reactions which can be quite disturbing to him and, at times, will evoke feelings of hostility within him.⁸ The parents might begin to blame all members of the medical profession as well as paramedical personnel for their child's problem, and to act in a very hostile fashion. The worst thing that a pediatrician can do in such circumstances is to react in kind. At the other extreme, some parents will react by either denying that any problem exists or by having their child institutionalized and informing both family and friends that he died. Fortunately, these are extremes, and some parents will even sublimate their problem in a most productive and useful way by directing their efforts toward establishing programs for the mentally retarded.⁹

The three fundamental questions mentioned above sum up most of the questions that parents will ask their physician. However, should

the pediatrician believe that, for personal or other reasons, he cannot face this problem, he should feel free to refer such cases to a qualified colleague or to one of the many diagnostic clinics available in most parts of the country.

"Why?" There are two facets to this interesting question. The first involves the etiologic factors of the child's mental retardation. It is here that the pediatrician, with his extensive organic and developmental background, is most competent and feels most comfortable. However, even here frustrations can arise, since in many cases the cause of the mental retardation cannot be uncovered even after the most sophisticated workup. Mental retardation which is diagnosed during the first two years of life is often of the most severe and obvious kind and ultimately the most likely to be labelled with a specific medical diagnosis. If it is the kind that does not become obvious until later, it is more likely to be less severe, not so readily apparent on casual observation, and also less likely to be specifically labelled. Even with the most sophisticated and extensive medical workup, a specific cause can be found in only about 20 to 25 percent of all cases of mental retardation.

The other aspect of the "why" question involves the deep-seated anxieties, fears and guilt feelings which all parents who are faced with this problem have in greater or lesser degree.¹⁰ These feelings will involve such matters as difficulties with in-laws and parents who opposed the marriage, doubts about the spouse's genetic background, and doubts about one's own abilities as parents, from the biologic as well as from the psychologic point of view. The physician needs to be aware of these feelings, but he must not interpret them as being the major contributing cause of the child's problem. If he does, he will only aggravate the insecurity that the parents already feel, thereby making it more difficult for himself but for the parents, too, to help the child. A classic example of this mistake is the once quite ordinary use of the term "refrigerated" with reference to parents of autistic children, the epithet carrying with it the implication that autism was the fault of the parents.

"Will it happen again?" This is a question that most parents can be expected to ask, particularly if they are young and the mentally retarded child is their first-born. It can be best answered if the

specific medical cause of the condition has been ascertained—phenylketonuria, for example, where the recurrence risk is known to be 25 percent. Without a specific medical diagnosis, however, this becomes a very difficult question to answer.

Details of genetic counseling have been set down most adequately elsewhere.¹¹ However, even geneticists need to remember some of the basic principles of parental attitudes in the field of mental retardation in order to cope with the complexities of genetic counseling. For instance, at times parents will come to a genetics clinic not so much to find out what the diagnosis is or to ask about the possibilities of recurrence, as to assess blame on either side of the family, to find excuses for not having other children, or even to find a reason for dissolving the marriage.

"What can be done for my child?" This is the most important question parents ask. Most pediatricians, however, lack knowledge about community services, special educational programs and public health and social welfare facilities, and find it almost impossible to answer. Physicians in general have a somewhat negative attitude toward mental retardation because of its chronic nature and their feeling that there is nothing that can really be done for such children. Although it is true that there is no cure once the condition has been well established, much can be done to help some of them to lead productive and useful lives within the limits of their capabilities. In evaluating the prospects, one should stress the positive rather than the negative aspects of the child's potential. A program of priorities has to be established, including fundamentals such as toilet training, dressing, and ambulation. Since nursery schools and public schools for the most part will not accept a retarded child who is not toilet trained, this is very often one of the most important training goals. Training in the fundamentals can be accomplished by utilizing the services of public health nurses, occupational, rehabilitation and recreational therapists and many other members of the paramedical professions. Such assistance can be sought from local medical centers, children's hospitals, local mental retardation service boards, and mental retardation regional centers.¹²

The following is a series of important guidelines to keep in mind when discussing the diagnosis and management of a retarded child with the parents.

Counseling takes time

Counseling parents of a retarded child cannot be accomplished in one visit. Since the condition is lifelong, the parents will need advice over a period of years. Each stage of the child's life may present different problems necessitating different approaches and solutions. One reason pediatricians find the needed counseling difficult is that, regrettably, economic considerations are such that they probably cannot spend several hours talking to the parents. Yet extra time spent initially can save much time that otherwise may have to be taken up later in answering questions piecemeal.

In recent years many diagnostic clinics and centers for the study of mental retardation have been established throughout the country. Unfortunately, all too often such centers have produced costly and elaborate workups which are turned over to the parents as a dismaying mass of information, with no provision for any follow-up care. Many such centers have adopted the so-called team approach to diagnosis and management, which though it has many advantages, also has the major disadvantage that there is often no single person to whom the parents can turn for advice and follow-up. Such clinics have been concerned more with placing a label than in helping the parents plan for the future. They have neglected the simple fact that parents cannot digest all the technical data supplied and are often in such a state of shock initially that they do not even hear most of what is being told them. Therefore, follow-up sessions are needed to repeat what has been said before, and to give parents a chance to ask questions.

Identify Major Concerns

In order to communicate effectively, one must learn to listen. The pediatrician must avoid talking too much. The parents must be allowed the chance to ask questions and ventilate their feelings. One of the best ways to identify the major concerns and questions is to find out how much the parents know about the child's condition and what they want for their child. Such information can readily be obtained by asking a few simple questions:

- *At what age level do you think your child is functioning?* This simple question can give the physician an idea as to how reality-oriented the

parents really are. Most parents have a clear grasp of the realities of the situation, and often their assessment will be the same as that of the pediatrician or the psychologist. A very unrealistic answer, on the other hand, indicates that either the parents do not see the gravity of the situation or that they are consciously or subconsciously avoiding reality. In such cases it might be necessary to follow the case carefully over a period of six months to a year to see if the parents become more aware of the child's slow development. One should never compel the parents to face reality when they are not ready to do so, for this will only create hostility and confusion in them and force them to turn elsewhere for help.

- *What do you think the future holds for your child?* The answer to this question will not only give further insight into the parents' reality orientation, but it will also indicate directions to be taken to avoid putting the child into situations which are non-productive or in which he will continually face defeat. The pediatrician will find out, for instance, whether the parents strongly desire to keep the child at home, and if they do he can avoid making recommendations which will oppose that plan.

- *What can we do for your child?* This question will often help identify the major concerns in question; and will also elicit the existence of various problems at home, not only with respect to the child's behavior and the problems surrounding the daily care of the child, but also with respect to some of the feelings the parents might have concerning the child's slow development, and the impact of the child's retardation on the family unit.¹³ This is important because any child is part of a family unit, and what he does or does not do affects every other member of that family group. It is well to remember at this particular point that when one talks about counseling parents, one clearly means both parents, not just the mother. In addition, in some cases it may be advisable to include teenage siblings, since the presence of a retarded sibling in their home can have an emotional impact upon them, and also can cause considerable anxiety with respect to future marriage and children.

The physician must avoid simply attaching a medical label and then telling parents there is nothing one can do. Nothing will more certainly

make "shoppers" of parents. Keeping the following points in mind will help in counseling and management:

- *Do what is best for the child.* This requires not only a complete evaluation of the child's potential but also the establishment of clearly defined training goals. Very often parents will need to have a strong guide in the management and care of their retarded child.¹⁴ Occasionally their guilt feelings will lead them to believe that the child should not be disciplined. In those circumstances he may become unmanageable. In more recent years the technique called behavior shaping or operant conditioning has come into prominence, mostly through the efforts of psychologists.¹⁵ Such techniques are now used not only by psychologists but by educators, public health nurses and social workers and they are based upon methods used by many parents in raising normal children—namely, that of rewarding good behavior and punishing or ignoring bad behavior. For this to be effective, however, one must establish a set of clearly defined rewards for clearly defined behavior, based upon the functional capacity of the child.

- *Help parents learn to live with the problem.* Basically mental retardation is a condition the parents can never really learn to accept; and because of this they will, in one way or another, search for the rest of their lives for answers and solutions. Most parents, fortunately, learn on their own what the best solutions are for them, and in so doing they often turn to family members, friends, and members of the clergy for assistance. How they eventually solve this problem depends upon their inner strength as individuals and upon the stability of their marriage. In-laws or other family members, when they enter into the picture, may sometimes give strength, sometime add to turmoil. Regrettably, a retarded child frequently becomes the straw that breaks the camel's back, causing a disintegration of an already fragile marriage.

There may also be social pressures which cause problems within the family. This is particularly true in the case of an upper middle-class professional or executive, who finds the presence of a retarded child in his household detrimental to his social success.

- *Seek help elsewhere.* Unfortunately, the pediatrician in practice does not have the advantages of the team (or multi-disciplinary)

approach through which diagnostic clinics and centers make use of the services of social workers, public health nurses, psychologists, psychiatrists, educators, and physical therapists. Hence they may think it advisable to refer such children to such a center. However, the practicing pediatrician often overlooks the fact that through his long association with the child and the family he has established a closer relationship with that unit than can possibly be achieved by a team. He should, therefore, feel free to take it upon himself to seek help through various social agencies as well as the regional centers which are now being established in many parts of the country to furnish services to retarded children. Such organizations can help him find placements outside of the home, if necessary, and also obtain nursery school placements as well as public school placements for such children.

The psychiatrist can be extremely helpful in dealing with the problem as a whole,¹⁶ particularly when unresolved guilt feelings and conflicts arise within the family. If appropriate, the pediatrician may sometimes also find it wise to refer the family to a member of the clergy for counsel and help.

Parents should be encouraged to join the many parent groups that have been established throughout the country, most of them under the jurisdiction of the National Association for Retarded Children. Often it is very helpful for mothers of mentally retarded children to meet and discuss their mutual problems. Furthermore, such parent groups often have established their own nursery school programs, workshops and school programs for retarded children, all of which can be of great help not only to the parents but also to the pediatrician.

Don't allow your own feelings to dominate. All too often a physician will tell the parent what to do with his child, basing his advice upon what he thinks he would do in a similar situation. This has led to the practice, unfortunately still prevalent in some areas of the country, of strongly recommending to parents that their child with Down's syndrome be placed outside of the home immediately after birth. Parents should be given alternatives, with both the positive and negative aspects of each alternative, and then they should be allowed to make up their own minds in light of their own particular needs.^{17,18} At no time should the physician literally command the par-

ents to do what he thinks is best. In the last analysis, the major consideration must always be what is best for the child, and although in one family situation it would be detrimental to have the child placed outside the home, in another family which is unable to cope with this problem and which is disintegrating in the face of it, placement of the child outside the home might be the wisest course.

In most families, merely presenting the options is sufficient. But where it is obvious that the family cannot make a decision, an experienced pediatrician might suggest what seems to him the best solution.¹²

Deal carefully with coping mechanisms. Regrettably, some parents enjoy infantilizing their child, and this may be for them a necessary coping mechanism to fulfill an inner need. (We see this sometimes not only in mothers of retarded but even of normal children.) Such mechanisms often have to be modified to some degree in order to help the child. However, at times we might be tempted to help a suffering mother by rearranging her life, forgetting that she is probably thriving to some degree upon that suffering. This is particularly true in cases of extreme symbiotic relationships which every worker in this field has seen in the course of his professional life. Attempting to break up such a relationship will very often result in profound disturbance in either one or both of the members of this relationship. Therefore, provided that this relationship does not interfere excessively with the child's well-being, it is best to let it alone.

Even with careful and thoughtful application of the foregoing, the practicing pediatrician unfortunately will not always be successful in the difficult task of counseling parents. Some parents are just not prepared to listen to any advice. They are the "shoppers," who are all too well known to clinics, medical centers and physicians in practice. Sometimes improper counseling in the beginning is at fault, but often it is simply that the parents do not wish to face the realities of the situation, and hope to find some kind of miraculous cure. Unfortunately, at times they end up in the hands of unscrupulous individuals and organizations who promise a lot but produce little.

In conclusion, it should be remembered that a mere medical diagnosis is not sufficient. A diagnostic label looks nice, and is rather satisfying

to us as professionals, and may be even interesting to the parents; but in the last analysis one must remember that we need to do what is best for the child, and this can be best accomplished by helping the parents learn how to live with this problem, plan for the child's future and help him achieve his maximum potential.¹²

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USE OF PROPHYLACTIC PACING CATHETERS

There are articles on the use of a prophylactic pacing catheter in acute myocardial infarction that conclude, "Why bother? Patients with inferior infarction who develop heart block do well and they don't need you; those with anterior infarction do badly and you can't do anything for them." I think we have passed the point where we have to be extremely discriminating about the insertion of a pacemaker. I submit that one ought to consider the insertion of a pacemaker as the conservative approach today. . . . I think that in a coronary care unit, with an adequate experienced staff, the insertion of a pacemaker is associated with a very low morbidity and certainly an extremely low mortality. It is a very awkward situation to find yourself in, that is, a patient who has developed a heart block and then develops irritability or one who has developed a second-degree heart block with an intermittent third degree and then develops ventricular prematures. You don't know whether the irritability is due to the bradyarrhythmia or to an irritable area in the ventricle, but if you institute therapy (lidocaine or whatever) there is a very real hazard that you'll eliminate this pacemaker focus if there is a third-degree block or cause a third-degree block in a second-degree heart block patient. We don't do things very well at three o'clock in the morning.

I think all these factors lead one to conclude that (given a good team) if you have a patient who develops third-degree block, whether anterior or inferior, inserting a demand pacemaker is a very conservative approach. . . . I say this realizing that what has been said in the literature about the accomplishments in anterior wall infarction may be true. This is a lot better way to go than to try to sit the patient out, introduce Isuprel® and all the rest of these things that are probably associated with a greater hazard than the pacemaker.

—EDWARD GENTON, M.D., Denver

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Medical Progress

Recent Advances in Neuroblastoma

JERRY Z. FINKLESTEIN, M.D., C.M., AND
GERALD S. GILCHRIST, M.B., B.CH.,
Los Angeles

■ *Neuroblastoma is one of the commoner tumors of infancy and childhood. There is great variation in the histological picture and even within one tumor. One unique feature is the apparently high rate of spontaneous regression, particularly during the first year of life. There is also a tendency for neuroblastoma to mature to the more benign ganglioneuroma and recent in vitro studies suggest that a serum factor may influence this process. Approximately 90 percent of patients with neuroblastoma excrete abnormally high quantities of various catecholamines, thus providing a useful diagnostic tool and a means for evaluating the effect of therapy.*

Treatment requires a multidisciplinary team approach involving a surgeon, radiotherapist and chemotherapist. Prognosis is influenced by a number of host factors and the most important of these seem to be the patient's age at diagnosis and the extent of the disease, although some children with widespread disease appear to have a particularly good prognosis. It is difficult to evaluate the influence of chemotherapy on survival in patients with neuroblastoma but it has not been of great significance. The unique biologic characteristics of this tumor require further study in the hope of providing more effective therapy.

NEUROBLASTOMA IS A MALIGNANT neoplasm arising from embryonic sympathetic neuroblasts and may originate from the adrenal gland or sympa-

From the Department of Pediatrics, Harbor General Hospital and University of California, Los Angeles, School of Medicine (Finklestein); and Childrens Hospital of Los Angeles and University of Southern California School of Medicine (Gilchrist). Dr. Gilchrist is now at the Mayo Clinic and Mayo Graduate School of Medicine, Rochester, Minnesota.

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Reprint requests to: J. Z. Finklestein, M.D., Department of Pediatrics, Harbor General Hospital, 1000 West Carson Street, Torrance, Ca. 90509.

thetic ganglia. With few exceptions it is a tumor of childhood and accounts for 8 percent of deaths from cancer in children. In children it ranks third in frequency to leukemia and central nervous system tumors.¹ Nevertheless, it is a rare condition and the yearly incidence ranges between 5 and 10 new cases per million children under 15 years of age.² Of 1,191 cases in the United States and Canada between the years

1961 and 1965, 30 percent occurred in the first year of life and the incidence declined exponentially with advancing age. In 19 cases the diagnosis was made at birth and nine more on the second or third day of life.³

This review is intended to summarize some recent advances in the understanding of the pathophysiology of neuroblastoma and to discuss newer concepts of treatment.

Pathophysiological Considerations

There is great variation in the histopathological picture from tumor to tumor and within the same tumor. At one end of the spectrum are undifferentiated cells which are very difficult to distinguish from those of small cell sarcoma and at the other end are tumors which consist solely of mature cell types. Between these two extremes the tumors may exhibit varying degree of differentiation.

Neuroblastoma and Ganglioneuroblastoma

Beckwith⁴ has devised the following histopathologic grading of neuroblastomas which includes the so-called ganglioneuroblastomas.

Grade I. Predominantly differentiated: over 50 percent differentiating elements.

Grade II. Predominantly undifferentiated: 5 to 50 percent differentiating elements.

Grade III. Slightly differentiated: under 5 percent differentiating elements.

Grade IV. Undifferentiated: no recognizable neurogenesis.

Histologic grade could be related to prognosis. In one series Beckwith found that five patients with Grade I tumor all survived beyond two years whereas three of four with Grade II tumor, four of 13 with Grade III and only one of 28 with Grade IV disease survived. Similarly the Surgical Fellows of the American Academy of Pediatrics found that approximately 30 percent of patients with well differentiated or moderately differentiated tumor survived beyond two years without evidence of disease compared with only 9 percent of those with poorly differentiated neuroblastoma.⁵

Ganglioneuroma and Maturation of Neuroblastoma

Ganglioneuromas represent the benign end of the neuroblastoma spectrum. The tumors are

usually circumscribed and encapsulated. Their extensions often project from the main tumor and tenaciously entwine adjacent structures. They are often calcified on roentgenography and can produce elevation in urinary catecholamine excretion.⁶

For many years controversy has existed regarding reports of maturation of neuroblastoma toward the more benign ganglioneuroma.⁷⁻¹² The maturation to the more benign form appears to parallel the natural embryogenesis of the sympathetic nervous system.⁷ Greenfield and Shelley reviewed 66 cases of neuroblastoma seen at the Johns Hopkins Hospital and found 11 cases with complete maturation to benign ganglioneuroma.¹² Virtually all reported transformed tumors have been found in a paravertebral position or some other extra adrenal location.^{11,12} The rationale behind Bodian's use of vitamin B₁₂ as therapy for neuroblastoma was that since the vitamin is essential for the normal maturation of hematopoietic cells, it might enhance the maturation of neuroblastic cells to ganglioneuroma.¹³ This approach has not been proved successful.

Further support for the concept of maturation has been the demonstration that immature neuroblastoma can differentiate into mature ganglion cells in tissue culture¹⁴ and the recent identification of a factor which selectively stimulates the growth of sympathetic and embryonic spinal sensory ganglia.¹⁵ This factor, a protein, was discovered by Levi-Montalcini and her coworkers and has been termed the nerve growth factor (NGF). It apparently exerts its effect by stimulating RNA synthesis and thus is specific in that tissues other than sympathetic and spinal sensory ganglia are not affected. Some of the biochemical characteristics of NGF have now been defined and because of its unique effect on cells of neural crest origin, intensive investigation has been undertaken of its role in the pathogenesis and maturation of neuroblastoma. Serum levels of NGF have been determined in a small number of patients with neuroblastoma, and elevated levels were found in some patients. Analysis of preliminary data is inconclusive with respect to the relationship between NGF and neuroblastoma regression. Further studies may provide additional insight into this and other factors which could influence the growth and maturation patterns of the tumor.

Neuroblastoma and Von Recklinghausen's Disease

Chatten and Voorhees¹⁶ in their study of familial neuroblastoma suggested the possibility that a developmental relationship exists between neuroblastoma and neurofibromatosis. This is supported by Bolande and Towler, who found ganglion cells or ganglioneuromatous tissue or both within the neurofibromas in six cases of Von Recklinghausen's disease.¹⁷ They also found ultrastructural similarities between neurofibroma and neuroblastoma maturing into ganglioneurofibroma. They theorized that neurofibromatosis may in some instances be derived from disseminated neuroblastoma or apparently migrating neural crest cells, particularly in the syndromes of congenital neuroblastomas with multiple skin and visceral metastasis.

Immunologic Aspects And Neuroblastomas *in Situ*

An important development in the study of neuroblastoma has been the demonstration of cell-bound immune reactions against host neuroblastoma cells when evaluated *in vitro*.¹⁸ Using a colony inhibition assay in which they are able to demonstrate immune reactions against human transplantation antigens, the Hellströms found that lymphocytes from patients with neuroblastoma inhibited colony formation by neuroblastoma cells. Lymphocytes from mothers of patients with neonatal neuroblastoma were also inhibitory in this system. This work suggests that tumor-specific antigens are present on neuroblastoma cells and that immune mechanisms could play a role in determining the natural history of the disease.

These observations could also partly explain why infants with neuroblastoma have the highest rate of spontaneous regression associated with any human cancer.¹⁹ It may also provide an explanation for the demonstration of small deposits of neuroblastoma tissue in approximately one in 200 autopsies performed on infants up to the age of three months.²⁰⁻²³ This is 40 times the expected rate based on the incidence of the tumor in the childhood population as a whole.²⁰ Additional evidence related to an immune reaction was provided by Martin and Beckwith, who found that lymphocytic infiltration within the tumor is associated with an improved prognosis.²⁴

One can therefore speculate that spontaneous

regression of overt tumor of neuroblastoma *in situ* is the result of a cell-mediated immune response. However, this does not provide an explanation of the high incidence of spontaneous regression and "cure" in infants, as compared with older children. One hypothesis relates to the reduced levels of humoral antibody in young infants and the possibility that the higher levels in older children could impair the accessibility of tumor cells to the lethal action of lymphocytes.

Biochemical Aspects

Since the cells of the sympathetic nervous system and chromaffin tissue of the adrenal medulla are capable of synthesizing and secreting various catecholamines it is not surprising that tumors arising from these precursors secrete excessive amounts of these compounds. Increased formation of dopa, dopamine, l-norepinephrine and their metabolites is said to occur in the majority of patients with neuroblastoma. Chart 1 outlines the relevant metabolic pathways, and demonstrates the wide variety of compounds which might be excreted in excess. These metabolites are identifiable in urine and although there is great variability in the relative excretion of each compound, one can expect that approximately 90 percent of patients with neuroblastoma will have elevation in the urinary levels of vanilmandelic acid (VMA) or homovanillic acid (HVA) or both.²⁶ Thus determination of these two catecholic substances would allow for identification of the majority of neuroblastomas without resorting to more elaborate biochemical procedures. In doubtful cases it may be advantageous to measure the excretion of the other products of dopa metabolism. Measurement of VMA and HVA excretion is not only helpful in diagnosis but can and should be utilized as an index of therapeutic effect since levels of excretion tend to parallel clinical evolution of disease.²⁶ However, it must be emphasized that one cannot distinguish between ganglioneuroma and neuroblastoma on the basis of catecholamine excretion pattern alone. Neuroblastoma and pheochromocytoma are both neural crest tumors and may excrete similar products of metabolism. One biochemical distinction relates to the fact that pheochromocytomas excrete only VMA and its precursors.

The prenatal identification of congenital neuroblastoma has been reported by Voute.²⁷ Six mothers presented with symptoms in the eighth

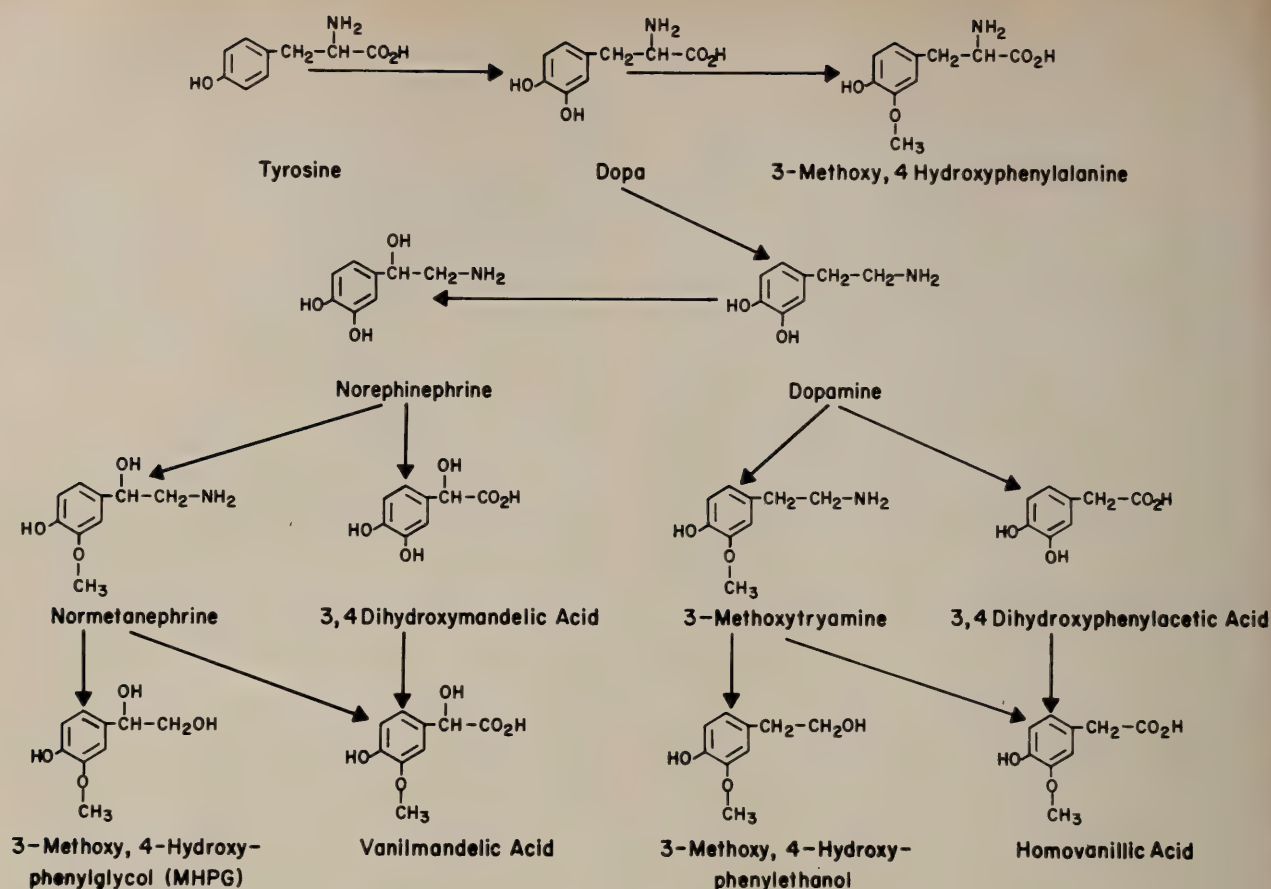


Chart 1.—Metabolic pathways in neuroblastoma (Williams and Greer²⁵).

or ninth month of pregnancy similar to those of adults with a pheochromocytoma. These symptoms appeared to be caused by fetal catecholamines entering the maternal circulation and included attacks of sweating, paleness, tingling of hands and feet, headaches, decreased sensibility in fingers and toes, heart palpitations and in one case paroxysmal hypertension. Their offspring, three boys and three girls, were diagnosed as having neuroblastoma between day one and nine months of age, (two at birth, one at six weeks, one at ten weeks, one at two months and one at nine months). All infants had increased levels of urinary excretion of catecholamine metabolites. The symptoms exhibited by the mothers during pregnancy suggest that neurogenic tumors were functioning within the fetus. Analysis of the urine and blood from mothers such as these should provide further information and urinary metabolites and catecholamines should be assessed whenever pregnant women exhibit the appropriate symptoms during the last months of pregnancy.

A method for rapid determination for catecholamines has been developed and could be adapted as an office procedure.²⁸ As recommended by Gitlow et al the test is performed as follows:

1. To 4 drops (0.2 ml) of urine in a graduated centrifuge tube add 10 percent potassium carbonate to the 3 ml mark.
2. Add 4 drops of an equivolume mixture of 0.1 percent para-nitroaniline and 0.2 percent sodium nitrite and shake mixture.
3. Add isoamyl alcohol to the 4.5 ml mark.
4. Shake tube for 1 minute.
5. Compare visually against the standard similarly prepared from normal urine to which 5 μ gm of VMA had been added.

A negative urine gives rise to a colorless pale yellow or orange upper layer (isoamyl alcohol), whereas a positive test is one in which this layer has a pink or violet hue equal to or greater than the VMA standard. All the agents must be refrigerated until immediately before use. Para-nitroaniline is made by dissolving 1 gram of

para-nitroaniline in 20 ml of concentrated hydrochloric acid diluted to 1 liter with distilled water. Sodium nitrite should be prepared freshly each month. For the VMA standard 10 mg of VMA is diluted in 500 ml of water and 5 drops or 0.25 ml is added to 4 drops of urine. This test has been reported to have given negative results in 62 children with miscellaneous tumors and positive results in 32 of 35 patients with neuroblastomas.²⁸

Cystathionine, an intermediate metabolite of methionine, is usually found in human brain, liver, kidney and muscle but is not normally present in urine. It has been detected in 50 percent of patients with neuroblastoma but its excretion appears to be independent of VMA, a fact which could make it a useful diagnostic test in the occasional patient in whom there is no elevation of urinary VMA or HVA. As with the catecholamines, its disappearance from the urine correlates well with clinical improvement.²⁹ D'Angio reported preliminary attempts to exploit the capacity of neuroblastoma to synthesize cystathionine from methionine through homocysteine by administering SE₇₅ labelled methionine to four children with metastatic neuroblastoma.³⁰ Localization of isotope using the scanning technique was seen within tumor three to six hours after the injection of the radionuclide in three of the patients. In two patients who underwent surgery, incorporation of the radioisotope was seen in excised tumor specimens. This procedure requires further investigation and may become an important diagnostic aid.

Clinical Staging of Neuroblastoma

Prognosis in neuroblastoma is related to age of the patient, the presence or absence of bone marrow metastasis, and the degree of differentiation of the tumor cells. Evans et al³¹ have proposed a staging scheme which describes the extent of the disease present without reference to resectability, because the latter includes the additional variables of surgical judgement and expertise. Where some authors tend to exclude children under one year of age from analysis because of the favorable prognosis in this age group and other authors include the degree of differentiation of the tumor, Evans acknowledges that the age of diagnosis does have prognostic significance but points out that it remains to be shown whether the extent of disease in infants influ-

ences their survival. She includes all neuroblastic tumors except pheochromocytoma and ganglioneuroma.

- Stage O: Neuroblastoma *in situ*
- Stage I: Tumor confined to the organ or structure of origin.
- Stage II: Tumor extending in continuity beyond the organ or structure of origin but not crossing the midline. Regional lymph nodes on the homolateral side may be involved.
- Stage III: Tumors extending in continuity beyond the midline. Regional lymph nodes may be involved bilaterally.
- Stage IV: Remote disease involving skeleton, organs, soft tissues, or distant lymph node groups, etc.
- Stage IV-S: Patients who would otherwise be Stage I or II but who have disease confined only to one or more of the following sites: liver, skin or bone marrow but without radiographic evidence of skeletal disease.

The proposed staging was applied to 100 children with neuroblastoma entered on two studies conducted by Childrens Cancer Study Group A. Short term survival data of this sample demonstrated the staging practical and it appeared to be of help in estimating prognosis. A special Stage IV category (IV-S) was developed because it was recognized that certain findings in children with neuroblastoma do not necessarily indicate as grave a prognosis as when similar circumstances occur in patients with other malignancies. Patients in the Stage IV-S category particularly those under 12 months of age have a good prognosis in spite of the widespread nature of the disease.³²

Treatment

Therapy directed against neuroblastoma must involve a multidisciplinary team approach. Surgeons, radiation therapists and chemotherapists all play a role in designing the treatment program even when one or other modality is not utilized in the initial plan of therapy.

Ideally, a tumor board consisting of representatives from the various disciplines should review each case from the point of view of adequacy of

diagnostic evaluation and in order to plan a rational and consistent treatment regimen. In this way, each patient derives the benefit of thorough review and ultimately enough data can be collected to allow for review of the success or otherwise of a particular program.

For convenience we will review the use of each of the current modes of therapy, bearing in mind that only close cooperation between the surgeon, radiation therapist and chemotherapist can result in optimal patient care. Since the approaches with x-ray therapy and surgical operation have been reasonably well standardized, they will be described first. The various drug regimens will be described and approaches being used by the various cancer chemotherapy groups will be outlined. Brief consideration will be given to an immunotherapeutic approach that might be used for treatment but must still be considered to be investigational.

Surgical Aspects of Therapy

Completion of the clinical investigations usually requires one to two days. Roentgenographic studies and catecholamine determinations usually provide confirmation of clinical impressions so that the disease can often be diagnosed preoperatively. Anemia, if present, is corrected by the administration of red cells before operation. In view of the variability of presentation, the role and extent of surgical operation must be assessed in each case individually.

Tumors should be completely excised although most surgeons do not advocate en-bloc dissection of contiguous viscera.³³ Whether operation alone should be considered as definitive therapy in cases where the tumor is completely resected remains to be determined, particularly in children under one year of age. The role of postoperative chemotherapy in this patient group is currently under investigation. Surgically resected localized disease in the infant does not appear to warrant postoperative radiation therapy, although this is also in dispute.

The high probability of early metastasis should not discourage a surgical approach unless x-ray study, bone marrow aspiration or lymph node biopsy confirms the widespread nature of the disease. Histologic confirmation of the diagnosis should be made but a marrow aspirate infiltrated with tumor cells in a patient with increased urinary excretion of HVA or VMA is sufficient to

diagnose neuroblastoma. Often, the resectability of the tumor can be assessed only after laparotomy or exploratory thoracotomy, at which time a biopsy in non-resectable disease is indicated. However, most radiotherapists and chemotherapists are in favor of removing bulk tumor, leaving minimal residual disease to treat. Thus surgical resection of as much of the tumor as possible is an acceptable and probably desirable procedure in children with neuroblastoma, if it can be accomplished without undue hazard. There is insufficient data to answer the question as to whether the removal of the primary affects the growth of metastatic lesions.⁵²

In addition to evaluation of the tumor from the viewpoint of resectability and the obtaining of adequate tissue for histological examination, the surgeon is in a position to provide information regarding extent of disease which may not be apparent from other diagnostic studies. Even in the presence of metastasis initial exploratory laparotomy, or thoracotomy, is often indicated with removal of bulk tumor and marking of residual disease with appropriate clips that can be followed postoperatively with roentgenologic studies. Control of disease as evidenced by improvement in clinical, radiologic, and biochemical parameters is often an indication for surgical re-exploration 12 to 18 months after the initial operation. At re-exploration the residual tumor, if any, is evaluated by biopsy and removed in toto, if possible.

Although there is little in the literature regarding complications secondary to anesthesia in patients with neuroblastoma, these patients can be a problem and blood pressure may have to be controlled with phentolamine. The preoperative use of an alpha adrenergic blocking agent such as phenoxybenzamine may be indicated.³⁴ Adrenocorticoid function may be depressed and additional hydrocortisone may be needed. Patients with secreting tumors may also need extra sedation in the preoperative period.

Radiation Therapy

D'Angio has emphasized that all tissue at risk must be included in the treatment field, but no more than this and he advocates the use of external heavy metal blocks to shape fields appropriately.³⁵ Radiation dosage is usually adjusted according to age and mid plain doses delivered in the abdomen using 250 kv techniques range

from 1800 rads to an infant of less than 12 months to 3500 to 4000 rads to a child 4 to 5 years of age.³⁵ The dose is delivered over a period of two and a half weeks to four and a half weeks, depending on the child's age.³⁶ Children with neuroblastoma confined to the primary and adjacent lymph nodes should have all areas of tumor included in the treatment field. In planning localized radiation therapy, each extra adrenal site relates to different organs or tissues whose tolerance must be considered. Growing cartilage and growing bones demand attention in all sites. It is usually not possible to completely resect an adrenal neuroblastoma and the radiation therapy recommended uses curative doses with the daily dose of radiation conditioned by the size of the field and the nature of complications. Radiotherapy is well tolerated by children in the immediate postoperative period, but it seems reasonable to permit the patient to recover for one or two days before instituting therapy. Many radiotherapists now recommend inclusion of the entire width of the vertebral body in the irradiated field in order to minimize the incidence of scoliosis which results from asymmetrical irradiation of the vertebral growth centers.^{36,37} However, even with this precaution, scoliosis can result from neurogenic involvement and fibrosis and contracture of soft tissues.³⁶ The liver can also be adversely affected by radiation as evidenced by reduced radioisotope uptake in areas included in the irradiation field. Tefft et al, in evaluating 115 children who received irradiation to the liver, found abnormalities in liver function with doses as low as 1200 rads.³⁸ The abnormalities appeared to be dose-related. Generally those patients who have abnormalities of liver function tests or liver scans in the acute phase will show some abnormalities in the chronic phase following irradiation. The incidence of severe clinical dysfunction in children is approximately 5 percent.³⁸ Care should be taken to exclude the kidneys from the direct radiation beam particularly if the contra-lateral kidney is outside the area of known tumor involvement. Should the kidneys both be involved one can consider attempting to shield one or both organs to limit the dose to within that tolerated by renal tissue. Another approach would involve attempting to eradicate the tumor using chemotherapy and thus eliminating the hazard of radiation nephritis.

Preoperative irradiation is not recommended since it tends to obscure the histological picture and we do not subscribe to the view that with such therapy more definitive surgical procedures can be undertaken. However, the approach can produce clinical regression of tumors and is advocated by Rissanen.³⁹ We consider that the patient with metastatic disease in whom surgical exploration is not contemplated is usually not a candidate for definitive radiation therapy until such time as chemotherapy or surgical operation or both have restricted the disease so that it is considered accessible to tumoricidal doses of radiation. In patients who have rapid development of spinal cord compression or in whom superior venacaval symptoms develop, high daily doses are warranted. A dose of 400 rads daily to a level of 1200 rads has been advocated by Young et al to assure rapid tumor shrinkage.⁴⁰ Increased edema concurrent with the radiation is not a major problem and the "field within a field technique" has been used to concentrate the dose to the critical area.

In cases of widespread dissemination, radiotherapy is administered with a palliative intent and is directed to either the primary site for control of symptoms as with bowel or bladder obstruction, intrathoracic problems or spinal cord compression. Palliative doses vary from 200 rads in one treatment to 600 rads in three consecutive days. However, as much as 2000 rads in 14 days may be required for relief of bone pain, treatment of localized or diffuse intracranial metastatic lesions, unsightly scalp masses, or control of intra-abdominal tumors.³⁶

Chemotherapy

The most widely used two agents in the treatment of neuroblastoma are cyclophosphamide and vincristine. These agents have been used alone in various dosage regimens or in combination as either sequential or alternating chemotherapy.⁴¹⁻⁴⁷

Following James' report in 1965 of 100 percent complete or partial remission rate in children⁴² of varying ages with unresectable neuroblastoma, it appeared that a highly effective combination of drugs was now available for treatment of this heretofore relatively unresponsive tumor. Unfortunately, using a similar regimen of alternating vincristine and cyclophosphamide in patients with metastatic disease, Evans et al, reporting for Chil-

drens Cancer Study Group A, found objective response in only nine of twenty-nine patients,⁴⁶ and of these only four were classified as attaining complete remission. Similarly disappointing results were reported by Sullivan et al in the Southwest Cancer Chemotherapy Study Group.⁴⁵ Certainly vincristine alone has been disappointing in this tumor system, as evidenced by remission rates of 22 percent in two independent studies.^{42,45} On the other hand, cyclophosphamide has produced a much higher response rate even when used in conventional dosage schedules of 2.5 to 5 mg per kilogram of body weight per day.⁴¹ Unfortunately these remission rates are deceptive since they relate to a temporary response; overall survival has not been significantly influenced by chemotherapy.

One approach is to administer larger amounts of an effective drug in order to obtain an improved therapeutic effect. The program is then limited only by an individual's tolerance to the drug. Whereas cyclophosphamide was usually administered in doses of 2.5 to 5 mg per kilogram of body weight per day, we have been impressed by rapid tumor shrinkage when doses of 10 mg per kilogram were administered daily either by mouth or intravenously.⁴⁷ Therapy is continued until the white blood cell count falls to between 1000 and 1500 per cu mm, which usually occurs in 10 to 14 days of treatment. Objective tumor regression was documented in nine of ten patients and complete remission occurred in eight. The treatment can be repeated every three to five weeks.

At present, drug treatment with cyclophosphamide alone or in combination with vincristine should be utilized in children with neuroblastoma. Whether or not infants with localized resectable disease should receive chemotherapy is a question currently being evaluated by Children's Cancer Study Group A.

In a situation such as this, where short-term responses to chemotherapy do not influence survival, a continuous search must be made for improved methods of treatment. A few new agents are under investigation; l-sarcolysin and duanomycin have been given to a small number of patients with no dramatic results. Thus far, they have not been shown to be equal to either cyclophosphamide or vincristine as active agents for children with neuroblastoma.⁴¹⁻⁵¹

Bodian in the early 1960s suggested that patients with neuroblastoma respond to therapy with vitamin B₁₂.¹³ A survey published in 1965 by Sawitsky and Deposito revealed that American investigators were not able to show any increase in remission rate with either vitamin B₁₂ alone or in conjunction with radiation therapy or other chemotherapeutic agents in patients with advanced disease.⁵² Recently the Medical Research Council in England sponsored an analysis of data from various investigators in the United Kingdom in order to evaluate the effect of vitamin B₁₂ in children with neuroblastoma.⁵³ This retrospective study failed to confirm that vitamin B₁₂ therapy is beneficial. Forty-three of 47 children whose treatment did not include vitamin B₁₂ were known to have died, compared with 56 of 61 children who received the vitamin in addition to other treatment. There appears to be no place for vitamin B₁₂ therapy in the modern approach to the treatment of neuroblastoma.

Immunotherapy

Stimulated on the one hand by the poor results with conventional therapy in neuroblastoma and by the evidence for the existence of antigens peculiar to the neuroblastoma cell on the other hand, various investigators attempted to develop treatment programs based on immunotherapeutic principles. Lymphocytes from mothers or older siblings have been infused into patients on the premise that these lymphocytes may react against the tumor cells, as has been suggested might occur on the basis of *in vitro* studies in other centers. Preliminary studies at the New York Memorial Hospital⁵⁴ and other centers will, it is hoped, provide data to support or refute this concept.

Treatment Programs Based on Staging

Stage I. Patients with localized disease should have the benefit of complete surgical resection, assuming that the primary site is technically accessible. Although many centers employ radiation or chemotherapy or both in this group of patients, control data is not available to either support or refute their use. If x-ray therapy is given it should be confined to the tumor bed, and postoperative chemotherapy should include cyclophosphamide in either conventional or high dose regimens for 12 to 18 months.

TABLE 1.—*Patients Surviving Two Years Free of Disease (From Breslow & McCann⁵⁵)*

<i>Age at Diagnosis (months)</i>	<i>STAGES</i>					
	<i>I</i>	<i>II</i>	<i>III</i>	<i>IV</i>	<i>IV-S</i>	<i>All stages</i>
0-11	11/12 (92%)	15/16 (94%)	2/4 (50%)	5/18 (28%)	18/19 (95%)	51/69 (74%)
12-23	3/4 (75%)	3/17 (43%)	5/8 (62.5%)	0/25 (0%)	1/3 (33%)	12/47 (25%)
24+	4/5 (80%)	4/12 (33%)	3/15 (20%)	3/93 (3%)	2/5 (40%)	16/130 (12%)
ALL AGES	18/21 (86%)	22/35 (63%)	10/27 (37%)	8/136 (6%)	21/27 (78%)	79/246 (32%)

Stage II and III. Patients with disease extending in continuity beyond the organ of origin are potentially curable. Surgical operation should be undertaken with a view to removing as much tumor as possible. It is extremely helpful in subsequent management if the surgeon has placed clips around the tumor bed or any area of residual area. Postoperative radiation therapy should be instituted but could be delayed in situations in which chemotherapy is to be used for tumor shrinkage when surgical removal was not accomplished. Chemotherapy utilizing cyclophosphamide with or without vincristine should be continued for at least 12 months.

Response to therapy is measured by clinical, radiological and biochemical factors. Those patients with primary tumors in the abdomen or pelvis who have responded to therapy and appear controlled are candidates for a "second-look" operation 12 to 18 months after the original surgical procedure.

Stage IV. Because of the widespread nature of disease in this group of patients, chemotherapy offers the only approach. Attempts at surgical resection or definitive radiation therapy cannot be expected to alter the poor outcome and these modes of therapy should be utilized for palliation only.

Stage IV-S. The accumulating evidence that these patients have an improved prognosis is apparently not related in any way to therapy. It appears logical to remove the primary tumor and administer chemotherapy postoperatively. Based on their review of 25 patients with Stage IV-S disease, D'Angio, Evans and Koop do not advocate radiation therapy and suggest that chemotherapy be considered only in patients with demonstrable bone marrow involvement.³² Unfortunately it is unlikely that more definitive evaluation of the role of therapy will be forthcoming in this group of patients, since they are

few in number and most are under one year of age and thus have a higher likelihood of spontaneous regression.

Prognosis

Survival is strongly influenced by the patient's age, extent of disease, degree of cell differentiation, the presence of skeletal and bone marrow metastasis. Breslow and McCann have analyzed data on 246 children, treated at the Childrens' Hospital of Philadelphia and in other institutions affiliated with Childrens Cancer Study Group A⁵⁵ (Table 1). Ninety-two percent of infants with Stage I disease survived, tumor-free, two years from diagnosis, compared with only 3 percent of those over 24 months of age with Stage IV disease. More than 50 percent of patients in this study had Stage IV disease and, irrespective of age, only 6 percent survived two years without disease. Thus for the majority of newly diagnosed patients the outlook is extremely poor. An improved prognosis has also been observed in patients with mediastinal primaries, but once again the major influence may be age, since most of the survivors tend to be in the younger age groups. Also there is a tendency for mediastinal tumors to be less undifferentiated and, as was mentioned previously, a number of investigators have been able to relate prognosis to the degree of histopathological differentiation.

To evaluate the impact of various modes of therapy on prognosis, a subcommittee of the Solid Tumor Task Force of the National Cancer Institute undertook a comparison of survival following treatment in children with neuroblastoma in each of two years, 1956 and 1962.⁵⁶ By 1962 the clinical use of vincristine and cyclophosphamide in patients with solid tumors was common. The data on patients from three chemotherapy study groups were considered together and there were no statistically significant differences in sur-

vival of children with neuroblastoma first seen in 1956 as compared with those diagnosed in 1962. The survival pattern of children with or without metastasis had not changed. Since radiation and surgical aspects of neuroblastoma management were considered to have been similar during the two study periods, it was concluded that the addition of new anti-neoplastic agents and the increased use of chemotherapy in 1962 had not improved the survival of children with neuroblastoma. Further investigation of the biological features of this unique tumor as well as the continued evaluation of new and improved methods of treatment must be pursued in order to improve the outlook for patients with this potentially curable neoplasm.

TRADE AND GENERIC NAMES OF DRUGS

<i>Oncovin</i> [®]	vincristine sulfate
<i>Cytosan</i> [®]	cyclophosphamide

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Specialty Conference

Early Diagnosis of Chronic Obstructive Lung Disease

Moderator: JOHN F. MURRAY, M.D.

Participants: RICHARD H. GREENSPAN, M.D., WARREN M. GOLD M.D.,
AND ALLAN B. COHEN, M.D.

From the Medical Service, San Francisco General Hospital; the Departments of Medicine and Radiology, and the Cardiovascular Research Institute, University of California, San Francisco.

DR. MURRAY: * This symposium will be devoted to the early diagnosis, treatment, and prevention of chronic obstructive lung diseases. The topic is a timely one because it has been said that we are in a virtual epidemic of these diseases, and, accordingly, they have assumed enormous medical, sociologic and economic importance. I say "these diseases" because chronic obstructive lung disease is really a generic term that includes at least four separate disease entities: pulmonary emphysema, chronic bronchitis, bronchial asthma, and, occasionally, bronchiectasis.

The fact that these fundamentally different disease processes were lumped together in a general category about 15 years ago is an indication of our ignorance at the time. They were classified together because they had many similar clinical manifestations, and they all manifested a common hallmark—obstruction to expired air flow. One of the important points that

we will emphasize in this symposium is that it is now possible by the application of sophisticated biochemical, radiographic, and physiologic studies to differentiate these separate entities.

The reason for stressing early diagnosis is shown in Chart 1, which depicts schematically the course of a patient with either chronic bronchitis or emphysema from its onset, through a period of increasing severity, until the death of the patient. Although good data on the natural history of these diseases are not available, there is evidence that in the later stages of the disorders there is a relatively uniform (linear) progressive decline in pulmonary function. If we extrapolate backward from the data obtained in the advanced stages of these illnesses, we can infer that their total duration is 30 or 40 years or longer. This assumption is supported by the pathologic studies of Kleinerman, Cowdrey and Stein.¹ When they examined the lung specimens of 101 subjects between the ages of 15 and 44 years who died suddenly from trauma or accidental death they found anatomic evidence of emphysema in the lungs of the youngest age group studied, and the extent and severity of these lesions increased with advancing age.

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*John F. Murray, M.D., Professor of Medicine and Member of Staff of the Cardiovascular Research Institute, University of California, San Francisco; Chief, Chest Service, San Francisco General Hospital, San Francisco.

Reprint requests to: J. F. Murray, M.D., Chest Service, San Francisco General Hospital, 1001 Potrero Avenue, San Francisco, Ca. 94110.

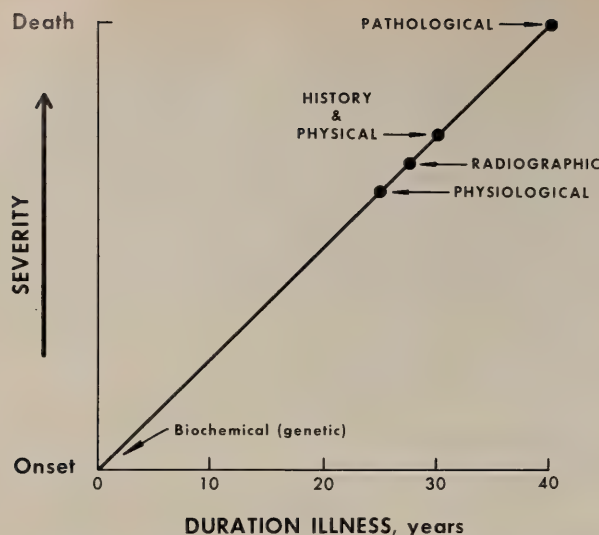


Chart 1.—A schematic depiction of the time-course of a patient with either chronic bronchitis or emphysema from the onset of the disease through a period of increasing severity to death. The earliest time when diagnosis is possible by various techniques is shown.

In the early 1900's the diagnosis of the various forms of chronic obstructive lung disease was uncommon and was determined largely by pathologists at the autopsy table. Even then the incidence of the disease was probably greatly underestimated, owing to faulty techniques of lung fixation and examination. In the 1930's and 1940's reliance was placed on conventional clinical techniques and it became evident that these allow us to diagnose the illnesses only when they are in an advanced state. Early diagnosis was impossible by these methods because, owing to the great reserve capacity of the lung, neither signs nor symptoms are produced until extensive parenchymal damage or airway involvement has occurred. Another point that we will emphasize in this symposium is that with new and available techniques of radiographic, physiologic and biochemical examination the diagnostic threshold can be lowered, permitting us to make the diagnosis much earlier in the long course of these illnesses. We believe early recognition will allow us to institute appropriate therapy that will forestall or retard the inexorable tendency of these diseases to progress. The first discussant is Dr. Richard Greenspan, who will comment on the usefulness of various radiographic techniques for the diagnosis of chronic obstructive lung diseases and describe the value of timed expiratory chest films for detection of obstructive pulmonary disease.

DR. GREENSPAN:† The chest roentgenogram is universally utilized to evaluate normal and abnormal morphologic features of the lungs. However, as a diagnostic test for the detection of obstructive pulmonary disease it is very crude. It is only of value in detecting advanced cases in which pronounced morphologic change in lung structure has already occurred. Roentgenographic-pathologic studies reported in the literature emphasize this point.²⁻⁶ Since the diagnosis of early obstructive lung disease depends on air-flow and volume studies, any single static measurement could be expected to be of limited value.

Comparison of a chest roentgenogram obtained during expiration with a standard inspiration film increases the sensitivity of roentgenographic diagnosis of obstructive pulmonary disease, but it is still only of value in moderately advanced and advanced cases. The main drawback is that the time required for the patient to expel air between inspiration and expiration remains unknown.

In an effort to increase further the sensitivity of radiography in diagnosing obstructive pulmonary disease, we developed a method to obtain timed films at full inspiration, at forced expiratory volume in 1 second (FEV_1), and at full expiration—the same measurements that are used clinically in screening for obstructive airway disease.⁷ A simple modification of a spirometer and an x-ray generator is utilized. The patient is first instructed on how to use a spirometer, and several control spirometers are obtained. He then stands in front of an x-ray film changer with the mouthpiece of the spirometer in place, and a full inspiratory chest roentgenogram is obtained. The patient then performs a forced vital capacity maneuver, blowing the air out into the spirometer. The timing device attached to the spirometer is automatically activated when expiration commences, and 1 second later a radiographic exposure is triggered (the FEV_1 film). The third chest film is taken on completion of the forced vital capacity maneuver. Thus, we not only have films taken at full inspiration, at FEV_1 and at full expiration, but we also have the spirographic trace, obtained simultaneously with

†Richard H. Greenspan, M.D., Professor of Radiology, University of California, San Francisco. The studies discussed herein were carried out in collaboration with Stuart S. Sagel, M.D. (NIH Fellow in Academic Radiology, GM 01272); James McMahon (Medical Student); and Gordon Gamsu, M.D. (Fellow of the James Picker Foundation).



Figure 1.—Timed expiratory chest films of a normal 35-year-old man. The majority of diaphragmatic motion occurs between the inspiration film and the FEV₁ film, during which time the patient expired 5.4 liters of air. Slight change occurs between the FEV₁ and the total FEV films, with another 0.6 liters of air being expelled. The mediastinum remains in the midline.

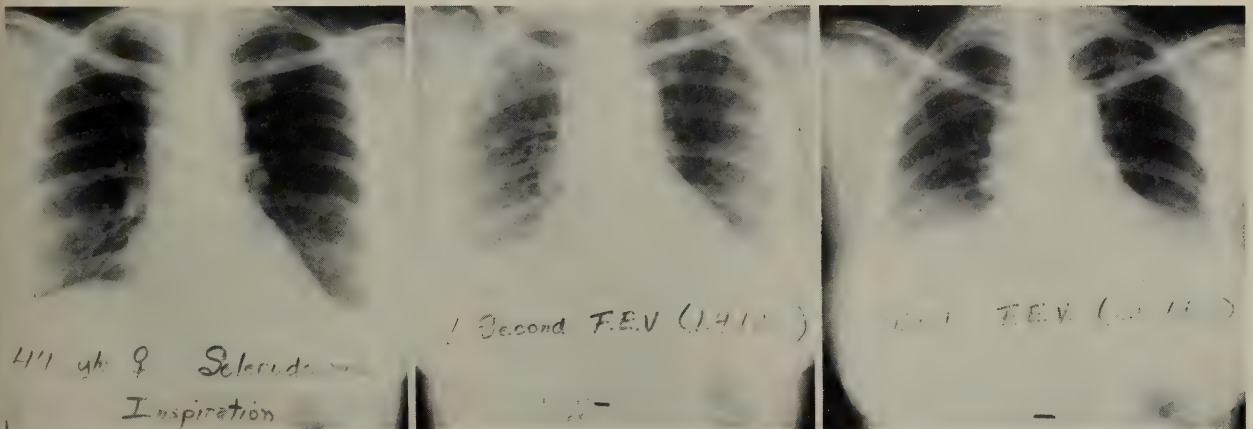


Figure 2.—Timed expiratory chest films of a 44-year-old woman with restrictive disease from scleroderma. Relatively little diaphragmatic motion occurs. The majority of the motion, however, is between the inspiration and the FEV₁ film. Total vital capacity is 2.0 liters. No mediastinal shift or evidence for localized air trapping is seen.

the roentgenograms, and a marker on the trace to ensure that the FEV₁ film actually was taken 1 second after start of expiration.

Although more than 150 patients have thus far been examined by this method, the films and spirographic tracings of only 90 have been carefully analyzed. The preliminary results in this pilot group indicate that this modification of standard x-ray techniques is of value. Of 28 normal control subjects, five had timed expiratory chest films indicative of either obstructive or restrictive pulmonary disease, which was subsequently confirmed by examination of the spirometric tracing. Forty-three of 44 patients with abnormal spirographic records had abnormal chest films as well. Six patients showed evidence

of localized trapping of air on the 1 second FEV film that could not be appreciated on either the full inspiration or full expiration x-ray examination; three of these had normal spirometric records.

In a normal subject, the major change in the position of the diaphragms and in the chest volume occurs between the inspiration and the FEV₁ films, with only a small change occurring between the FEV₁ and expiration films. The diaphragms rise evenly, and the lungs become evenly opaque. The mediastinal structures remain in the midline (Figure 1). Care must be taken to ensure that the subject exhales to maximum vital capacity while the films are being taken. The spirographic record obtained simul-

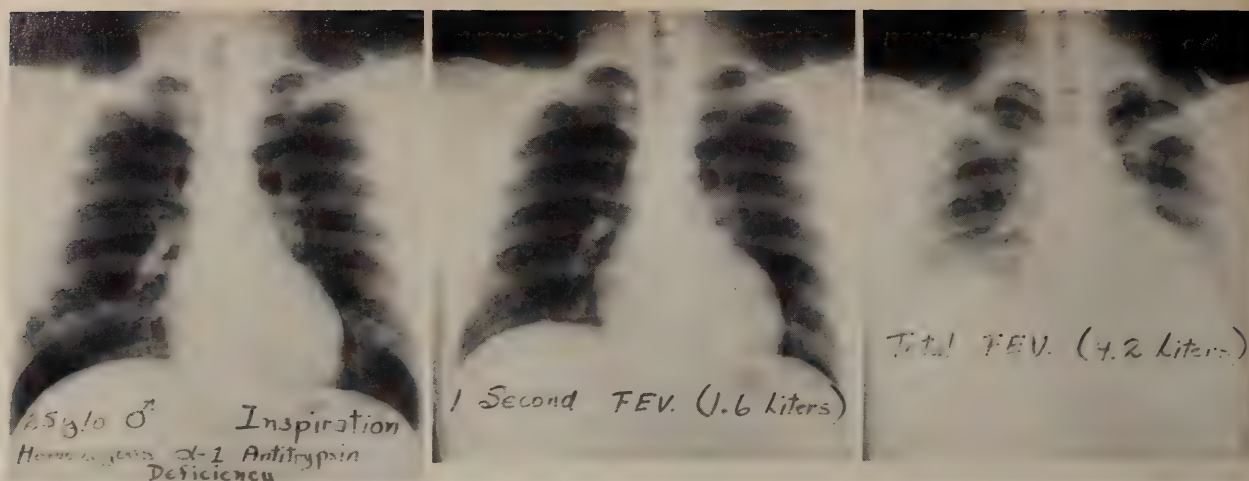


Figure 3.—Timed expiratory chest films of a 25-year-old man with diffuse obstructive airway disease associated with homozygous alpha-1-antitrypsin deficiency. The inspiration film is essentially normal. The total vital capacity is within normal limits as well (4.2 liters). A simple inspiration and expiration film on this patient would not reveal an abnormality; however, the FEV₁ film shows poor diaphragmatic motion compared with the inspiration film, and only 1.6 liters of air have been expired. No evidence of localized air trapping is seen.

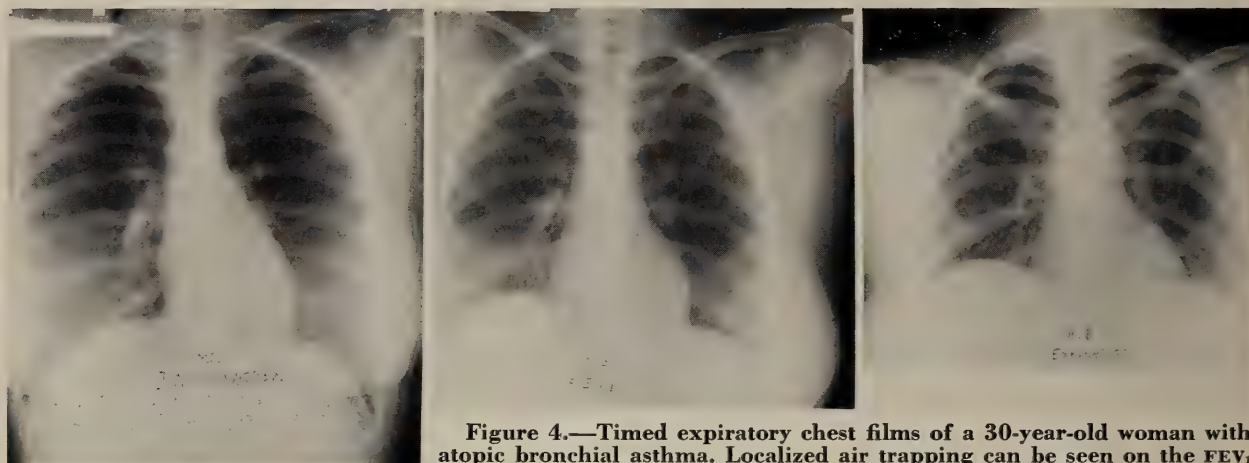


Figure 4.—Timed expiratory chest films of a 30-year-old woman with atopic bronchial asthma. Localized air trapping can be seen on the FEV₁ film on the left side. The diaphragm remains depressed, and there is a slight shift on the mediastinum to the right side. The left lung remains lucent, particularly in its lower portion. The full expiration and the inspiration films are normal, and the patient's spirographic tracings are also normal.

taneously with the x-ray exposures is compared with the control spirographic record obtained prior to the actual examination. Three false-positive readings, suggesting obstructive disease, resulted from lack of a full expiratory effort by the patient during the film exposure; these were easily detected by comparison with the spirographic records.

Restrictive disease is detected by diminished excursion of the diaphragms (Figure 2). As in the normal subject, the majority of diaphragmatic movement occurs between the inspiration and the FEV₁ films; however, the total movement is diminished.

Diffuse obstructive airway disease is mani-

fested by less motion between the inspiration and FEV₁ films and more diaphragmatic elevation and decrease in size of the chest between the FEV₁ and the full expiration roentgenograms (Figure 3). If the increased airways resistance involves the lung fields in a relatively even fashion, symmetry of the diaphragms and the midline position of the mediastinum are maintained.

Localized trapping of air is easy to detect by this method and may occur in the presence of a normal vital capacity and FEV₁. If the trapping is marked, it will manifest itself by a retention of lucency in the zone of trapping on the FEV₁ film and the full expiration films. Frequently there will be diminished or lack of motion of one dia-

phragm and shift in the mediastinum away from the involved area. If, however, the trapping of air is incomplete, it may only be apparent on the FEV₁ film, and the full inspiration and full expiration films may be normal (Figure 4). Thus, incomplete localized obstruction of airways can be detected by this method.

A large number of measurements are currently being made from the films and correlated with the spirographic tracings and with determinations of lung volumes obtained by physiologic measurements. In addition, planimetric determinations of lung volumes from the films⁸ are being correlated with plethysmographic determinations of lung volume. The number of measurements made thus far is not large enough to present at this time.

We think that this timed expiratory technique holds promise of being a simple and practical method that will enable radiologists to detect obstructive pulmonary disease at a considerably earlier stage than is currently possible. They should also be able to detect restrictive disease, and complete and incomplete localized zones of air trapping. We hope that analysis of various measurements made from the films and comparison of those to measured lung volumes will permit radiologists to make an estimate from the roentgenograms of lung volumes at full inspiratory capacity, FEV₁ and residual volume.

I will now ask Dr. Warren Gold to discuss the early diagnosis of chronic obstructive lung disease by physiologic techniques.

DR. GOLD:† For the last ten to fifteen years, pulmonary physiologists have spent many hours applying sophisticated physiologic tests to the evaluation of patients with severe end-stage obstructive lung disease. This approach is analogous to trying to determine the particular pathogenic pathway by which Bright's disease of the kidney develops. In fact, the study of end-stage pulmonary disease has provided very little information about the particular pathway by which the lung is finally destroyed. Our concern, as Dr. Murray indicated in his introduction, has been with the use of sophisticated techniques of physiologic evaluation of the lungs that may be abnormal in the face of unsuspected chronic pulmonary disease. Furthermore, we have been

NORMAL

ADVANCED EMPHYSEMA

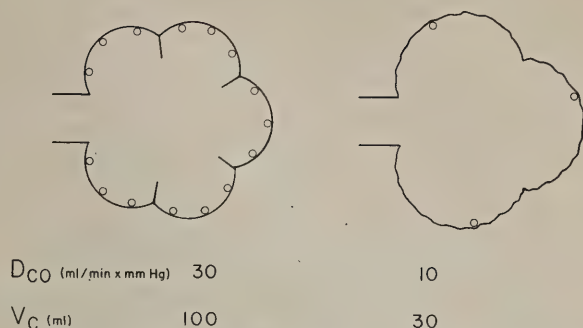


Figure 5.—Schematic models of the single breath carbon monoxide diffusing capacity (D_{CO}) and the pulmonary capillary blood volume (V_C) in the normal lung and in the advanced stage of emphysema. In the normal lung the alveoli are clustered about an alveolar duct leading into an airway; the open circles represent patent pulmonary capillaries. The lung of a patient with advanced emphysema is characterized by a decrease in the number of pulmonary capillaries, disruption of the normal architecture with a decrease in the number of alveoli, and an increase in the size of the remaining alveoli. Representative values for D_{CO} and V_C are shown for each of these conditions in the lower half of the figure.

concerned with the development of physiologic methods to differentiate the different types of diseases now lumped in the single clinical classification of chronic obstructive pulmonary disease. Figure 5 illustrates a model of the lung that we have found useful in the analysis of the abnormalities of structure and function of patients with emphysema. On the left is the normal arrangement of alveoli clustered about an alveolar duct leading into an airway. On the right are illustrated the destructive changes that develop in the case of advanced emphysema: The number of patent pulmonary capillaries is decreased, the number of alveoli is decreased, and the architectural framework is destroyed resulting in air spaces of abnormally large size with a decrease in elastic recoil properties. All of these features of emphysematous lungs have been described previously by pathologists.

Physiologically, these abnormalities would result in a decrease in the capacity of the lung to transfer gas from air spaces to the remaining pulmonary capillaries. In the laboratory we can measure the capacity of the lung to transfer a test gas (carbon monoxide) from the air spaces to the pulmonary capillaries.⁹ Furthermore, we can subdivide this total capacity (DL_{CO}) and actually measure the volume of blood contained in the pulmonary capillaries. If, in emphysema,

†Warren M. Gold, M.D., Assistant Professor of Medicine and Associate Member of the Cardiovascular Research Institute, University of California, San Francisco. The studies discussed herein were carried out in collaboration with J. A. Nadel, M.D., A. Gelb, M.D., H. Bruch, M.D., and R. Wright, M.D., at the Cardiovascular Research Institute, University of California, San Francisco.

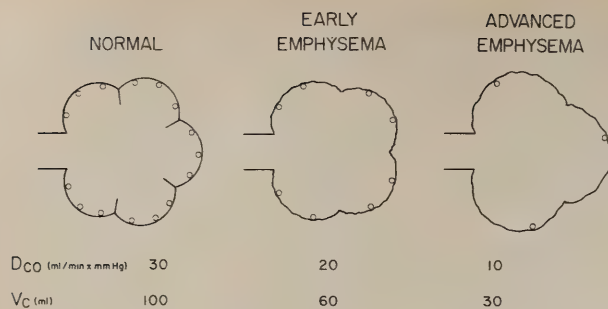


Figure 6.—Schematic models of the single breath carbon monoxide diffusing capacity (DCO) and the pulmonary capillary blood volume (V_C) in the early and advanced stages of emphysema (see Figure 5). Representative values for DCO and V_C are shown for each of these conditions in the lower half of the figure.

there is a decrease in the pulmonary capillary bed, then there will not only be a decrease in the DL_{CO} , but also a decrease in pulmonary capillary blood volume (V_C) (Figure 5). These tests can be carried out in the laboratory rapidly, simply, and painlessly without needles or catheters and without discomfort to the patient. However, we are concerned with detecting abnormalities in asymptomatic patients with emphysema. Figure 6 illustrates the abnormalities to be expected in the lungs of a patient with early, less-severe emphysema. Even in this situation, we would postulate that the alveolar capillary surface would be reduced, resulting in a decrease in DL_{CO} and V_C .¹⁰⁻¹³

The second major feature of the emphysematous lung is a loss of elastic recoil. One can think of lung parenchyma as behaving as if it were composed of a set of springs that resist stretching. As lung volume is increased, increasing pressure is generated by the parenchyma to cause the lung to recoil to its residual volume. If the increase in lung volume continues, an increased elastic recoil pressure will be generated. The relationship between elastic recoil pressure and lung volume is illustrated in Figure 7. In contrast to the normal lung, the emphysematous lung has a set of "sprung" springs. The lung does not resist attempts to distend it with the same recoil pressure as the normal lung. This abnormality results in a shift in the elastic recoil curve to the left of the normal curve illustrated by the dashed line in the figure. This curve shows that the elastic recoil pressure is decreased at every lung volume while the slope of the pressure-volume curve is increased. The slope of the recoil curve, or lung compliance, is defined by

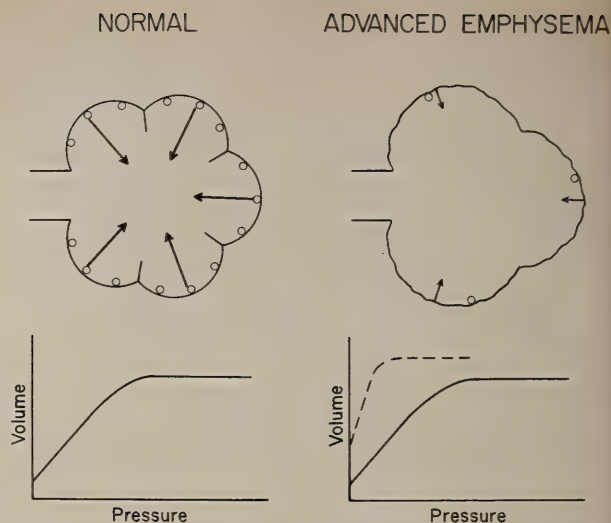


Figure 7.—Schematic models of lung elastic recoil in the normal lung and in the advanced stage of emphysema. The arrows represent the elastic recoil pressure generated by the lung, and the length of the arrow is proportional to the recoil pressure generated. Elastic recoil curves for each model are shown in the lower half of the figure. (Ordinate = lung volume; abscissa = elastic recoil pressure; solid line = normal lung; dashed line = advanced emphysema.)

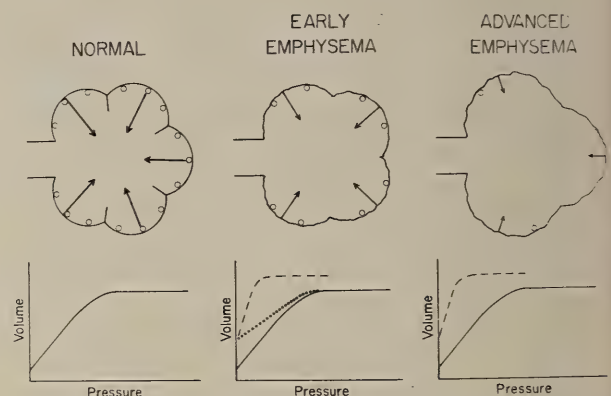


Figure 8.—Schematic models of lung elastic recoil in the early and advanced stages of emphysema. Elastic recoil curves for each of these models are depicted in the lower half of the figure. (Dotted line = early emphysema; see Figure 7 for explanation of other symbols.)

the change in lung volume divided by the change in recoil pressure. Lung compliance is a measure of lung distensibility, and as the recoil characteristics of the lung decrease, distensibility increases in patients with emphysema.

Figure 8 illustrates the changes in the elastic recoil behavior of the lung at an earlier stage of development of the emphysematous lesion. The elastic recoil curve of a lung with early emphysema might be represented by a composite of a normal curve representing normal regions of

lung and an abnormal curve representing the emphysematous regions of the lung. Consider the behavior of such a lung as it is inflated from residual volume to total lung capacity: With the application of a small pressure (for example, 5 cm H₂O), almost all of the emphysematous regions of the lung would inflate completely, but very little volume change would occur in the normal regions of the lung. In fact the normal regions of the lung would not become fully inflated until a pressure of 20 or even 50 cm H₂O had been applied. As indicated by the dotted line in Figure 8, at low lung volumes the curve reflects the emphysematous regions with a loss of recoil pressure, whereas at high lung volumes the curve reflects the more normal regions of the lung that have recoil characteristics closer to the normal range.¹⁴⁻¹⁶

On the basis of our knowledge of the pathologic changes in emphysematous lung, it appears that two types of tests would be useful in evaluating patients with this disease: (1) the transfer capacity for carbon monoxide (DL_{co}) and (2) the lung elastic recoil curve. To measure lung elastic recoil, however, we must approximate pleural pressure with an esophageal balloon. To avoid the minor discomfort associated with swallowing the esophageal balloon, we have tried to develop other less uncomfortable methods. One alternative approach is based on the fact that a large portion of the airways as well as the parenchyma of the lung are contained within the thorax, as indicated in Figure 9. These intrathoracic airways are subjected to the same distending pressure in the pleural space as the lung parenchyma. When there is a loss of lung elastic recoil, as in patients with emphysema, the negative pressure in the pleural space at a given lung volume is less than in the normal chest. As a result, the intrathoracic airways are subjected to a smaller distending pressure and, consequently, the airways of the emphysematous lung are narrower than those of a normal lung at the same volume. This change in airway geometry results in a pronounced increase in airway resistance since resistance is inversely proportional to the fourth power of the radius.

We have taken advantage of the effect of loss of lung elastic recoil on airway resistance by measuring the resistance to airflow at different lung volumes using a body plethysmograph. The relationships are illustrated in Chart 2. Nor-

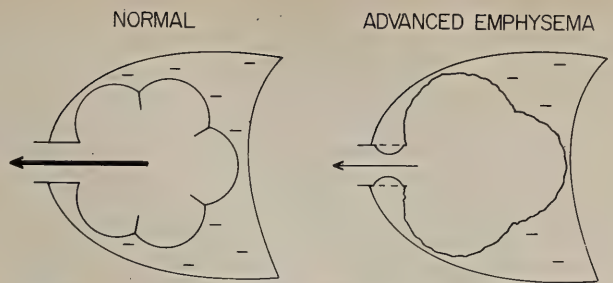


Figure 9.—Schematic models of the effect of loss of lung elastic recoil on airway geometry. The model of a normal lung shows the alveoli clustered around the alveolar duct communicating with an airway and contained within the chest wall. The pressure inside the chest but outside the lung (pleural pressure) is negative (shown by — symbols in pleural space), and acts not only to distend the parenchyma but to dilate the intrathoracic airways. The model of advanced emphysema illustrates a relatively less negative pleural pressure at the same lung volume. This results in less support for the intrathoracic airways leading to airway narrowing. The result is a decreased flow (decreased arrow in the airway) because of an increase in airway resistance.

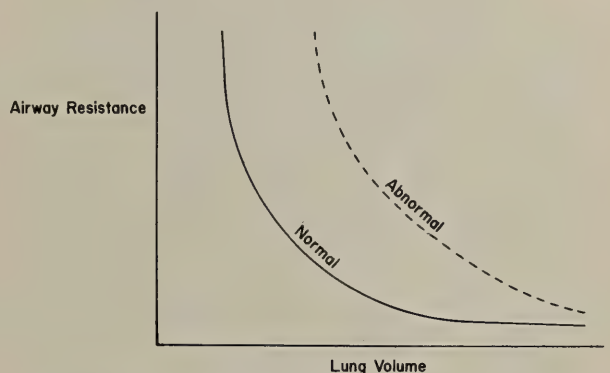


Chart 2.—Relationship between airway resistance and lung volume. Total lung capacity is at the right of the volume axis, residual volume at the left of the volume axis. (Solid line = normal lung; dashed line = abnormal or emphysematous lung.)

mally, airway resistance does not change greatly from total lung capacity to functional residual capacity, but from functional residual capacity to residual volume the resistance increases considerably. We believe this increase in resistance reflects the fact that residual volume is determined by airway closure. Therefore, the nearer the patient breathes to his residual volume, the more the airways are narrowed and the greater the increase in airway resistance. In a lung with a loss of elastic recoil, the diminished support of the intrathoracic airways causes the airways to narrow prematurely at a relatively large lung volume; concurrently, airway resistance increases prematurely as lung volume decreases.

Since a patient with early emphysema has an abnormal elastic recoil curve at low lung vol-

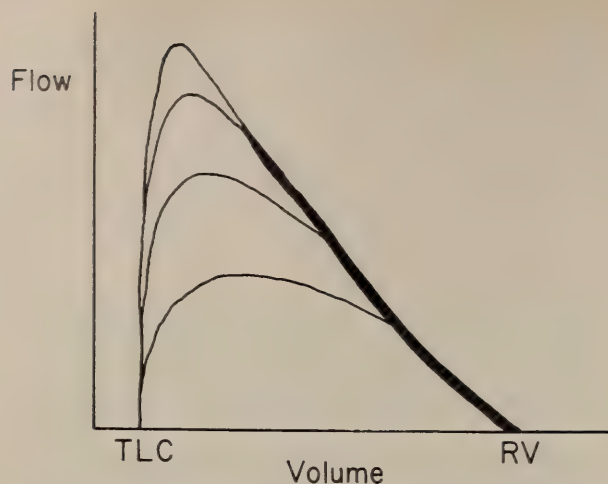


Chart 3.—Relationship between maximal expiratory flow and lung volume. The series of four curves, which start at total lung capacity (TLC) and end at residual volume (RV), represent repeated measurements of flow-volume curves with progressively increasing effort in one normal subject.

umes only, we predict that the resistance-volume curve is abnormal primarily at low lung volumes; in fact, the airway resistance might be perfectly normal at functional residual capacity or any higher lung volume. Although this measurement is easier to perform than that of lung elastic recoil, it does require cooperation on the part of the patient. Many patients with obstructive airway disease find it particularly difficult to breathe at low lung volumes when airflow resistance is greatly increased. We therefore examined other methods that would be more comfortable but would yield information reflecting the loss of elastic recoil properties.

In our laboratory, the best screening procedure to evaluate the mechanical properties of the lung is to measure the relationship between maximal expiratory airflow and lung volume (flow-volume curve).^{17,18} There are a number of spirometers on the market at present that provide a signal representing expired volume as well as another signal representing the flow rate at which the gas leaves the lung and enters the spirometer. These relationships can also be measured by a body plethysmograph, but this requires more technicians and money. In measuring flow-volume curves, the patient takes a deep breath to total lung capacity and breathes out while flow and volume are recorded. The maneuver is then repeated with still greater effort until finally the patient exhales with as much effort as possible as illustrated in Chart 3.

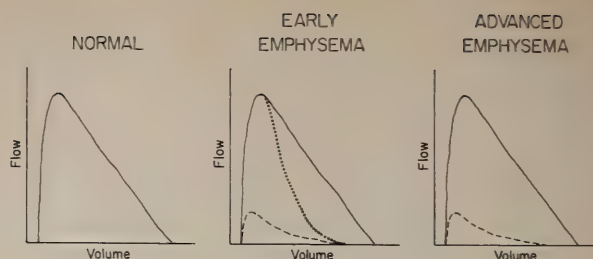


Chart 4.—Representative flow-volume curves in normal subjects and in patients with early and advanced stages of emphysema. (Solid line = normal lung; dashed line = advanced emphysema; dotted line = early emphysema.)

The resulting outer envelope of this series of curves defines the maximal expiratory air flow that can be generated at any particular lung volume. There are a number of important features of this curve: During the first 20 percent of the expired volume, the maximal air flow rate is dependent on the effort generated by the subject. This means that during exhalation of the first 20 percent of the total expired volume, the harder the subject tries, the greater the flow rate he achieves. Once he has exhaled the first 20 percent of the vital capacity, however, the flow rate during the remaining portion of the vital capacity is effort independent. This is indicated by the fact that all of the curves converge to form the heavy envelope in Chart 3.

Two variables determine this flow-volume envelope: (1) Maximal flow rate at a given lung volume is directly proportional to the elastic recoil pressure generated by the lung at that lung volume. If there is a loss in elastic recoil, there is a reduction in the maximal expiratory flow rate. (2) Maximal expiratory flow also depends on airway geometry. If the airways are abnormally narrow, then there is a reduction in the maximal respiratory flow rate. In patients with emphysema, these two variables are interrelated: The loss of lung elastic recoil not only decreases the driving pressure producing flow at a given lung volume, but also alters airway geometry so that flow is reduced because the airways are narrowed. Chart 4 illustrates the changes expected in the flow-volume curve in patients with advanced emphysema and in other patients with early emphysema. In the advanced stage of the disease, the decided loss in lung elastic recoil at all lung volumes greatly decreases the driving pressure and narrows the airways, resulting in a decrease in maximal expiratory flow rates at all lung volumes.

TABLE 1.—Results of Preoperative Pulmonary Function Studies in a 52-Year-Old Man

Pulmonary Function Study	Predicted	Observed
<i>Lung Volumes</i>		
Vital Capacity (L)	4.7	5.1
Total Lung Capacity (L)	7.1	7.1
Residual Volume (L)	2.4	2.5
<i>Lung Mechanics</i>		
Forced Expiratory Volume, 1 sec (L)	>3.3	3.3
Maximal Expiratory Flow Rate (L/min)	350-500	330
Airway Resistance (cm H ₂ O/L/sec)	0.7-1.8	1.4
<i>Diffusion</i>		
D _{lco} (ml/min/mm Hg)	34	15.4

At an earlier stage of this disease, the changes in the flow-volume curves would be slightly more complex: At high lung volumes, where the recoil characteristics of the lung are virtually normal, driving pressure and airway geometry would be normal so the maximal flow rates generated would probably be within the normal range. At low lung volumes, on the other hand, when the elastic recoil is decreased, maximal expiratory flow would be decreased owing to both the reduction in driving pressure and the narrowing of the airways.

Let me apply this theory to a clinical problem. A 52-year-old carpenter was referred to the hospital last year because of low back pain. He had smoked one package of cigarettes daily for 20 years but denied respiratory symptoms. A chest roentgenogram revealed a nodule in the upper lobe of the right lung. Preoperative pulmonary function studies are shown in Table 1. The normal vital and total lung capacities ruled out a restrictive pulmonary defect. The normal FEV₁, maximal expiratory flow rates, and airway resistance suggested that he did not have airway obstruction. The striking abnormality in these screening studies was the pronounced decrease in DL_{co}. There are two possible causes for such an abnormality: (1) vascular disease involving the microcirculation of the lung, or (2) emphysema with destruction of the pulmonary capillary bed.

We were able to differentiate these two possibilities by examining the flow-volume curve shown in Chart 5. The flow-volume curve obtained in the patient is compared with that of

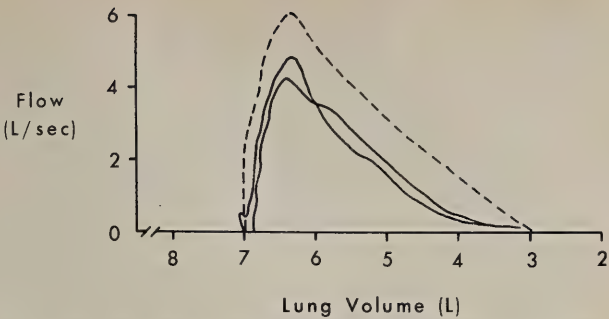


Chart 5.—Maximal expiratory flow-lung volume curve in a patient with clinically unsuspected emphysema. (Solid line = patient with unsuspected emphysema; dashed line = curve obtained in a healthy man of comparable age.)

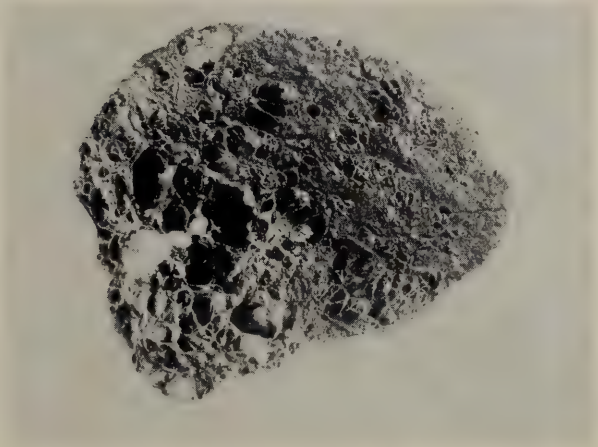


Figure 10.—Right upper lobe resected from patient with clinically unsuspected emphysema (mid-left). This is a cut section through a formalin-fixed lobe inflated with 25 cm of water pressure.

a healthy man of the same age with a comparable lung volume. Although there was a slight reduction in peak flow rate at total lung capacity, the patient was able to generate a peak flow rate of 5 liters per second (or 300 liters per minute), which is practically normal for a man of his age. The striking abnormality in the patient's flow-volume curve occurred at a low lung volume: the absolute flow rate was decreased and the curve became qualitatively different from the normal curve. Instead of flow decreasing linearly with volume, the curve became concave upwards. On the basis of the decrease in DL_{co} and the abnormal flow-volume curve, we predicted that when the lobe was resected the pathologist would find emphysema. Figure 10 shows a cut section through the formalin-fixed inflated lobe, revealing severe emphysema throughout the specimen.

Not only can physiologic studies detect the presence of emphysema when it is clinically un-

suspected, but physiologic studies can differentiate different kinds of obstructive airway disease. In a group of patients with "chronic bronchitis" Macklem's group found obliterative bronchitis involving small airways of 2 mm in diameter or less.¹⁹ In the human lung, the peripheral airways of 2 mm in diameter may be the only site of pathologic change. In this kind of peripheral airway disease, the small airways may be virtually completely obstructed, yet careful anatomic studies of inflated lungs from such patients reveal that the regions of lung distal to the obstructing lesion are ventilated and not atelectatic.²⁰ These anatomic studies indicate that collateral ventilation to the region of lung distal to the site of obstruction is sufficient to maintain normal expansion of the parenchyma.

The problem then is to determine what effect such a lesion would have on pulmonary function. Morphometric studies by Weibel suggest that approximately 90 percent of the resistance to airflow resides in airways larger than these 2 mm airways.²¹ Physiologic studies by Macklem and his colleagues²² confirmed the anatomic findings of Weibel. As Mead indicated in a recent editorial in the *New England Journal of Medicine*, small airways contribute so little to total airway resistance that substantial decreases in cross sectional area of these airways could occur in this kind of disease with only small and perhaps even undetectable influence on total airway resistance.²³ Hence, the usual tests of pulmonary function could be normal. Macklem and Mead demonstrated that despite the small contribution of such small airways to total airway resistance, the patency of small airways has a critical effect on the distribution of volume within the lung.²² For example, if 50 percent of the bronchi at the 2 mm level were obstructed, total airway resistance might increase only five percent, but lung distensibility or compliance would be halved. Following this suggestion, Woolcock and co-workers studied a group of patients with bronchitis and found a change in lung distensibility.²⁴ In addition, they observed that the effect on lung compliance could be magnified by more rapid breathing—that is, with increasing respiratory frequency, lung compliance decreased (Chart 6.)

The basis for this observation is illustrated in Figure 11. In this model, the intrinsic elastic properties of the lung units are equal, but the airway to one of the units is narrowed. Under

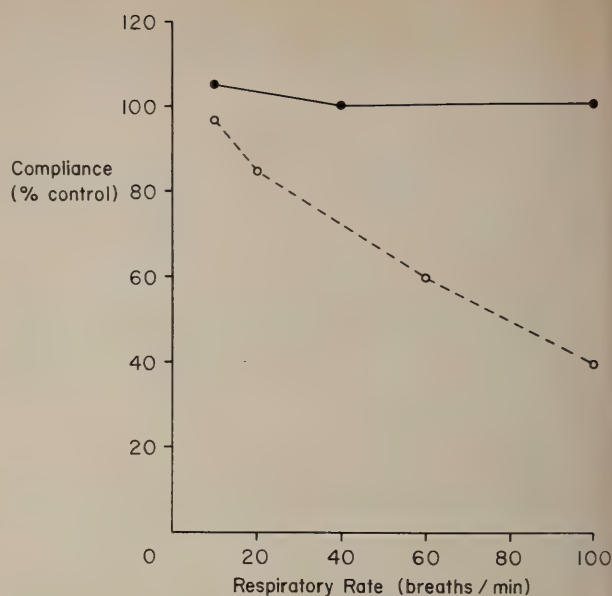


Chart 6.—The effect of respiratory rate on lung compliance. The solid line shows the effect of increasing respiratory rate in a healthy subject and indicates that lung compliance in healthy subjects is relatively independent of increasing respiratory rate. In contrast, the dashed line shows the results in a patient with peripheral airway disease and indicates that the lung compliance decreases decidedly with increasing respiratory rate in this condition.

dynamic conditions, the tidal ventilation passes preferentially to the unit with the patent airway. As the respiratory rate increases, this tendency increases, but as the rate increases, a greater fraction of the driving pressure dissipates in overcoming the resistance to airflow, leaving a decreasing pressure available to inflate the lung units. Thus, as the respiratory rate increases, the volume change produced by the inflating pressure diminishes and the dynamic lung compliance decreases. Since this lesion does not affect the lung parenchyma, the DL_{co} and static lung elastic recoil remain normal.

Table 2 summarizes the physiologic differences between emphysema and peripheral airway disease. In early stages of emphysema, there is a decrease in diffusing capacity and pulmonary capillary blood volume associated with a loss of lung elastic recoil, particularly at low lung volumes. This results in an increase in airway resistance and a decrease in maximal air flow rates, particularly at low lung volumes. The two screening studies that are most useful in making this diagnosis are the DL_{co} and the flow-volume curve. The physiologic diagnosis of peripheral airway disease is based on the following criteria: The DL_{co} , the pulmonary capillary blood vol-

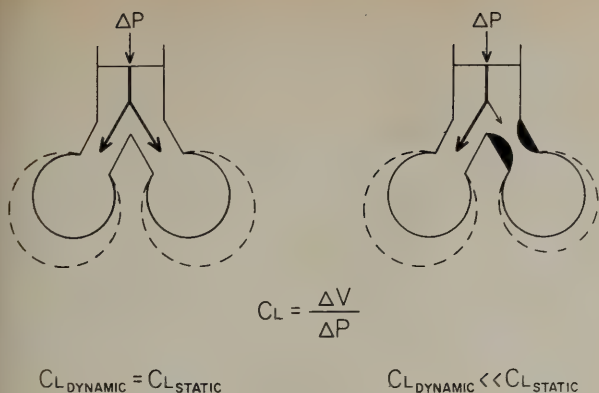


Figure 11.—Effect of peripheral airway obstruction on dynamic lung compliance. The effect of inflating the lung with a fixed, driving pressure (ΔP) is illustrated in a normal lung (left) and in a lung with peripheral airway disease (right). In the normal lung, the change in volume (dashed lines) produced by a change in transpulmonary pressure is similar under static and dynamic conditions up to respiratory rates of about 100 breaths per minute. In peripheral airway disease, although the intrinsic elastic recoil properties of the lung units are normal and equal, the airway to one of these units is narrowed. Under static conditions, the change in lung volume would be independent of the pressure of the airway obstruction, but under dynamic conditions, the tidal ventilation passes preferentially to the unit with the patent airway. As the respiratory rate is increased, a greater fraction of the driving pressure (ΔP) will be dissipated in overcoming the resistance to air flow, leaving a decreasing pressure available to inflate the lung units. Thus as respiratory rate increases, the volume change (dashed lines) produced by the inflating pressure diminishes and the dynamic lung compliance decreases. The amount of air flow entering the air space is indicated by the size of the arrow within the airways.

ume, and the static elastic recoil curves are normal, but the dynamic compliance decreases during rapid breathing.

Thus, physiologic tests of pulmonary function can be used to detect obstructive pulmonary disease when it is clinically unsuspected and, in addition, these tests may be useful in differentiating different types of chronic obstructive pulmonary disease.

At this point I would like to turn the session over to Dr. Allen Cohen, who is going to try to take us to an even earlier point in the obstructive pulmonary diseases by discussing recent biochemical advances concerning the diagnosis and clinical significance of alpha-1-antitrypsin.

DR. COHEN:§ Alpha-1-antitrypsin (A1T) deficiency is the only biochemically defined genetic defect that has definitely been related to emphysema. For this reason, A1T deficiency has

§Allen B. Cohen, M.D., Assistant Professor of Medicine, University of California, San Francisco; Director of Respiratory Intensive Care Unit, San Francisco General Hospital.

TABLE 2.—Summary of Physiologic Differences between Emphysema and Peripheral Airway Disease

Early Emphysema	Peripheral Airway Disease
$\downarrow D_{LCO}$ and pulmonary capillary blood volume	Normal D_{LCO} and pulmonary capillary blood volume
At low lung volume	Normal elastic recoil (static)
\downarrow elastic recoil (static)	\downarrow Compliance (dynamic)
\uparrow resistance	
\downarrow maximal flow rates	

been the subject of a great deal of research and controversy. Some of this controversy has made the literature difficult to interpret and one's own laboratory tests difficult to evaluate.

Alpha-1-antitrypsin is an alpha-1-globulin, which means that it migrates between albumin and alpha-2-globulin in routine electrophoresis of serum proteins. It has a molecular weight of 58,000 and is similar in many respects to albumin; however, it has a unique feature that has been of great interest to investigators in this area: it inhibits proteolytic enzymes. Alpha-1 is an appropriate name for this protein but antitrypsin is not. Trypsin is only one of many enzymes inhibited by A1T. Some of the many other proteolytic enzymes inhibited by A1T are elastase, chymotrypsin and leukocyte fibrinolytic enzymes.

The relevance of A1T to clinical disease is controversial. Eriksson,²⁵ the investigator who described A1T deficiency, studied a large population in Sweden, where such investigations are possible because of the relative immobility of the people. In a random sample of the population he found an incidence of approximately 0.05 percent for the homozygous disease state. The presence of the heterozygous gene was diagnosed by an intermediate level of A1T half way between normal and homozygous. He found a 4.7 percent incidence of the heterozygous gene. This study is unassailable in terms of demographic design and application of demographic mathematics. However, some of the more sophisticated techniques of physiologic assessment of lung function and evaluation of the phenotypes of A1T deficiency were not available to Eriksson at that time. Since then, Kueppers, Fallat and Larson²⁶ and Lieberman, Mittman and Schneider²⁷ have applied newer techniques of assessing pulmonary

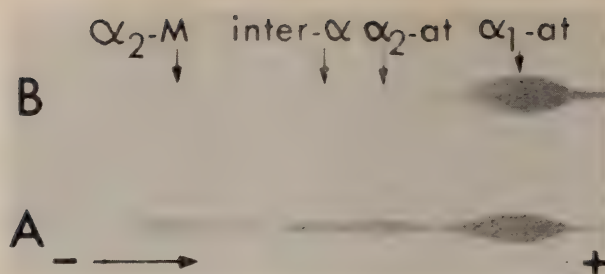


Figure 12.—Fibrin agar electrophoresis of serum from a heterozygote for the common α_1 -antitrypsin gene before (A) and 3 days after the injection of typhoid-paratyphoid vaccine (B). The dark areas indicate where the fibrin has remained undigested by trypsin due to the presence of trypsin-inhibitors in the different electrophoretic regions. (α_2 -M = α_2 -macroglobulin, inter- α = inter- α -trypsin inhibitor, α_2 -at = α_2 -antitrypsin, α_1 -at = α_1 -antitrypsin.) Note the large zone of inhibition due to increase of α_1 -antitrypsin in B, whereas the size of the zones of inhibition due to the other inhibitors has remained unchanged. (From Kueppers²⁸)

function to patient populations in Northern and Southern California and have come to different conclusions. Kueppers et al²⁶ used crossed gel electrophoresis, which will be discussed later, and found that approximately 25 percent of the patients with obstructive lung disease had either heterozygous or homozygous α_1 IT deficiency, whereas Lieberman et al²⁷ concluded that patients under the age of 40 years with emphysema have approximately a 50 percent incidence of α_1 IT deficiency. These studies have a problem, too, because the investigators were unable to carry out the kind of large scale demographic study that was possible in Sweden. In the Swedish studies there was no increase in the incidence of emphysema in patients with the heterozygous state. I think each of the studies has certain problems built into it, and that the relationship between the heterozygous state and emphysema has to be considered an open question.

There are several laboratory methods for evaluating α_1 IT. The first one I will mention, which is used by Kueppers,²⁸ is not useful diagnostically, but is helpful in understanding the trypsin or fibrinolytic inhibitory capacity of human serum; Figure 12 shows the different serum proteins that inhibit fibrinolytic enzymes.²⁸ Fibrinogen in an agar gel is put on a microscope slide. Trypsin is added to the gel and when the fibrinogen is digested, the gel becomes translucent. Serum is electrophoresed in a separate starch gel, and this gel is laid on top of the fibrin-agar gel. The separated serum components diffuse into the fibrin-agar gel. Trypsin is then added to the fibrinogen

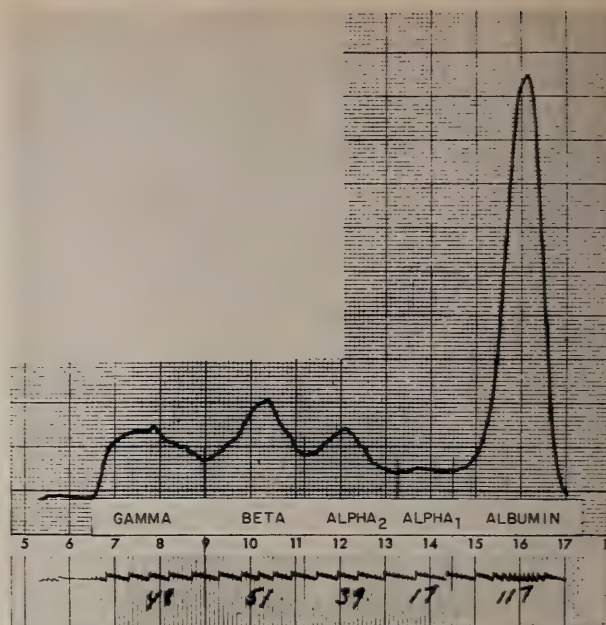


Figure 13.—Paper electrophoresis of serum proteins. Absence of α_1 -globulin peak in homozygous α_1 -antitrypsin deficiency, with a spuriously normal quantitative measurement of the α_1 -globulin is seen. Protein values were as follows: total, 7.3; albumin, 3.14; α_1 -globulin, 0.460; α_2 -globulin 1.044; β -globulin 1.365; and γ -globulin, 1.292 gm/100 ml. (From Lieberman, Mittman, and Schneider²⁷)

gel and the gel clears everywhere except in the area containing the inhibitors from serum. Therefore, the dark areas represent those serum proteins that inhibit trypsin. In normal human serum α_1 IT contributes most of the antitryptic activity, but at least four other antitrypsins are also present.

The diagnostically useful tests for α_1 IT deficiency can be divided into three major categories. One category measures by simple serum electrophoresis the entire class of proteins to which α_1 IT belongs. The second category measures the specific protein α_1 IT either quantitatively or qualitatively. The qualitative test is the best way to diagnose the heterozygous state at the present time. The third category measures the function of the protein.

Serum protein electrophoresis is the most widely available test (Figure 13).²⁷ Albumin migrates farthest, then α_1 IT; gamma globulin is at the anodal end. The α_1 IT is represented on the electrophoretic pattern by a peak that is a little bit smaller than alpha-2 but the alpha-1 peak is absent in sera from a patient with a homozygous deficiency of α_1 IT. Fallat* has pointed out (per-

*Robert Fallat, M.D., Chief, Chest Diseases, Pacific Medical Center, San Francisco.

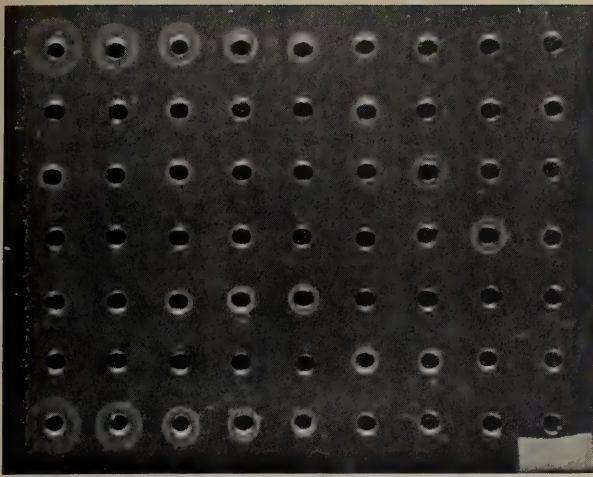


Figure 14.—Quantification of alpha-1-antitrypsin by radial diffusion. Serial dilutions of the standard were added to the top and bottom rows of holes. Concentration of alpha-1-antitrypsin is proportional to the log of the radius.

sonal communication) that it is well worth while to look at the electrophoretic pattern yourself because if the baseline is not set exactly right, a normal level of A1T can be reported even when the A1T peak is absent. Lieberman and associates²⁷ reported that you can also diagnose the heterozygous patient with this method, but better techniques are available.

Figure 14 depicts a method that is employed currently for quantifying the amount of A1T in serum. An aliquot of melted agar is cooled to a temperature that will not destroy antibodies; antibodies specific for A1T are then mixed into it. The agar is then poured onto a glass plate and holes are cut in the agar. A standard serum with a known concentration of A1T is diluted serially. The diameter of the precipitin disk is compared with the concentration and the standard curve is drawn; the diameter of the unknown disk is then used to calculate the concentration of A1T. The biggest problem with this technique is the requirement for standards of known A1T concentration. The laboratory must start the assay with purified A1T in order to have an appropriate standard. With the purified standard, one can make other standards that do not have to be pure. The problem is the purification of A1T. Kueppers was able to purify A1T while he was at the University of California in San Francisco, so there are reasonable standards in some of the local laboratories. Reports of studies in which this technique was employed must state exactly how the standards were derived; standards ac-

quired from commercial laboratories cannot always be relied upon.

The cross gel electrophoresis is also based on detecting the A1T specifically, and it also uses an antibody to A1T. Normal serum is electrophoresed in starch gel. The gel containing the electrophoresed serum is then cut out and placed on a plate similar to the one discussed earlier, only the agar has antibodies in it. Then the electrophoresed serum is reelectrophoresed into the agar. The precipitates that form in the gel are characteristic of different phenotypes of A1T (Figure 15).²⁹ The phenotypes of A1T act as co-dominant alleles. There is only 1 locus for the A1T gene, but it seems to control a complicated pattern demonstrated on the cross gel electrophoresis. In more recent work, Fagerhol and Laurell³⁰ found that there are many more bands on the crossed gel electrophoresis than were previously described. The important phenotypes are shown in the top row of Figure 15. The MM phenotype is the one most commonly seen, and the others are standardized by this third peak. The other peaks are standardized by the location of this peak. The FF phenotype migrates faster in the electrical field. This property gives this phenotype its name. The ss is a slow variant in this phenotype. The major band is slower than the major band in the MM phenotype. zz is the homozygous deficient phenotype, and the other patterns shown in Figure 15 occur in different kinds of heterozygous A1T deficiency states. Crossed gel electrophoresis is quite complex, but it has certain advantages over the other methods and is the only way to diagnose a patient's A1T phenotype.

The trypsin activity is then tested to see how much of it has been inhibited. In the radial diffusion technique, the standard deviations are broad and the heterozygote and normal phenotypes may be difficult to differentiate. Both the trypsin inhibitory capacity and the radial diffusion tests are less than perfect methods of diagnosing heterozygotes, but because of their simplicity they are the main tests in current use. Another problem with the trypsin inhibitory capacity is that A1T is only one of the proteins in human serum that inhibits trypsin. The test is still reasonably good because A1T makes up 90 percent of the normal trypsin inhibitory capacity of the human serum. Another major problem in using either the trypsin inhibitory capacity or the

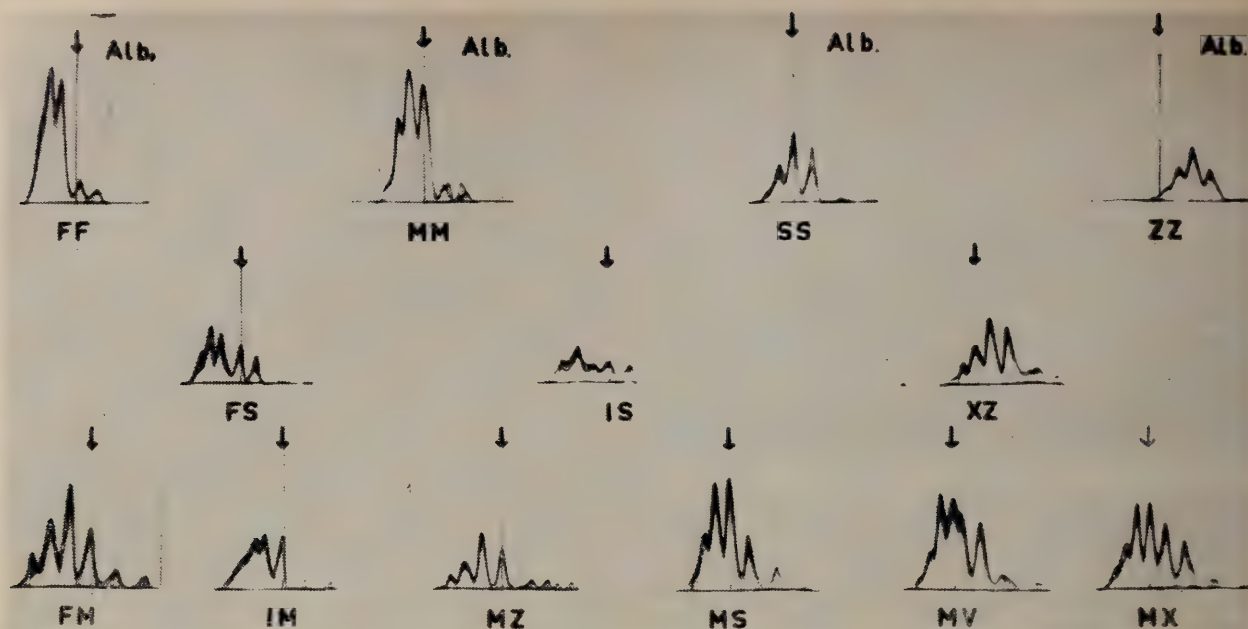


Figure 15.—The immunoprecipitation pattern after antigen-antibody crossed electrophoresis of sera with different α_1 -antitrypsin phenotypes. Initial separation is by discontinuous starch gel electrophoresis (pH 4.95). The antiserum in the agarose-contained anti- α_1 -antitrypsin and antialbumin (upper series) or only anti- α_1 -antitrypsin (middle and bottom series). The arrow above each vertical line marks the position of band 4 of phenotype MM. (From Fagerhol and Laurell²⁹)

quantitative ALT concentration tests, usually carried out by the radial diffusion method in diagnosing the heterozygous state, is illustrated by an interesting experiment performed by Kuipers (Chart 7).²⁸ A pyrogen, in this case parathyroid vaccine, was given to volunteers with homozygous, heterozygous, or normal genotypes for ALT. The level of ALT did not increase in the homozygous ALT-deficient patients under the stress of fever, but ALT increased to the normal range in the heterozygous patients. This means that the patient with bronchitis or emphysema who has an infection might have a normal trypsin inhibitory capacity and a normal level of ALT and yet be a heterozygote. For this reason crossed gel electrophoresis is currently the most reliable test for diagnosing the heterozygote. Certain other states, such as pregnancy, can also raise the heterozygous levels into the normal range.

In the San Francisco Bay Area both the trypsin inhibitory capacity and the radial diffusion quantitation tests are performed in the laboratory of Dr. H. H. Fudenberg at the University of California, San Francisco. The radial diffusion test is also performed in the laboratory of Dr. R. Fallat at the Pacific Medical Center, who is particularly interested in receiving serum specimens from physicians in the Bay Area. The cross

gel electrophoresis test is being developed in both laboratories but it is not yet available to physicians for routine studies.

There are several clinical characteristics of the patient with ALT deficiency. The major clue is the familial incidence, although other forms of emphysema also have a familial incidence.³¹ Another important clue is the onset of emphysema at a young age, since several studies indicate that people who have clinical emphysema by the age of 40 have a higher incidence of ALT deficiency than other emphysematous patients. In addition, the chest radiograph of a patient with emphysema due to ALT deficiency frequently shows evidence of a basilar distribution of bullous emphysema.

Finally, there are many current hypotheses as to the cause of emphysema in patients with low levels of ALT in their serum. Most hypotheses start with the relatively good assumption that the cause of emphysema is related to a function of ALT that we know about—that is that ALT inhibits proteolytic enzymes. The hypotheses are as many as there are investigators. Alpha-1-antitrypsin operates on both ends of the coagulation system and inhibits thrombin and plasmin, so a coagulation defect of some kind, such as pulmonary capillary occlusive disease, could perhaps

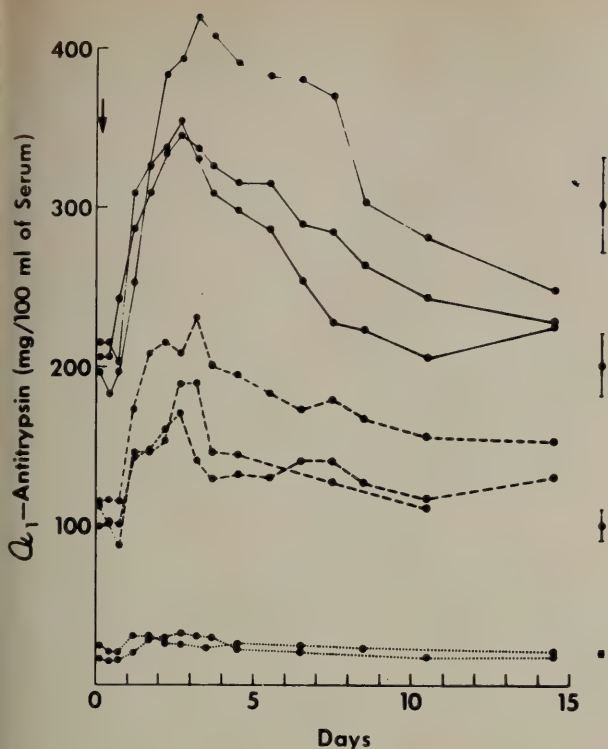


Chart 7.—Changes in α_1 -antitrypsin levels of serum following the intravenous injection of 0.2 ml typhoid-paratyphoid vaccine (arrow) in the genetically different individuals. (Homozygotes for common gene = solid line, heterozygotes for α_1 -at deficiency gene = dashed line, homozygotes for deficiency gene = dotted line.) (Standard error of the method is at the right.) (From Kueppers²⁸)

predispose to emphysema in these patients. Other investigators, Lieberman among them, have stressed the inhibition of fibrinolytic enzyme in leukocytes by ALT. Lieberman suggested that enzymes from the leukocytes are not inhibited in the lungs of these patients and therefore they digest lung tissue. Gross and coworkers³² produced emphysema in experimental animals by injecting papain down the trachea; in just a few days an emphysema-like condition developed. The short time necessary to cause these changes makes this a poor model of emphysema, but it looks pathologically very much like the human disease. The predominant line of thinking is that some kind of proteolytic destruction occurs that the patient is unable to combat.

Dr. Murray will now deal with the most difficult parts of this discussion: What is the major advantage in making an early diagnosis, and what can one do for his patients once he has established the diagnosis?

DR. MURRAY: Even though we now move from

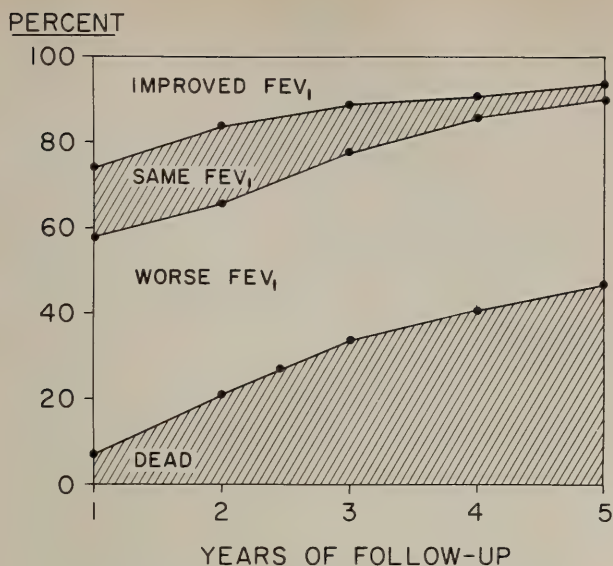


Chart 8.—Overall course of FEV₁ in 200 patients with obstructive lung disease. (From Burrows and Earle³³)

the realm of science to the realm of speculation, it is crucial that we address ourselves to two questions that are inevitable corollaries to the efforts toward early diagnosis. First, what treatment can we offer either to the patient in whom emphysema or chronic bronchitis has been detected early, or to the patient who has a biochemical abnormality that we believe predisposes him to the development of these diseases? Second, and an even more crucial and difficult question to answer, what influence do therapeutic interventions have on the natural history of these diseases? We are able to offer recommendations for preventive measures based on very plausible assumptions about the pathogenesis of these diseases, but our state of knowledge at present is so incomplete that we are unable to document what effect these maneuvers have on the subsequent course of asthma, pulmonary emphysema, and chronic bronchitis.

Perhaps the best way to approach the problem is to examine what is known about the natural history of advanced lung disease. Chart 8 reproduces data from a prospective study by Burrows and Earle³³ of 200 patients with chronic obstructive lung disease who were observed for at least five years. During the period of observation, about 40 percent of the patients died and most of the remainder had a progressive worsening of their FEV₁, indicating an increase in severity of their obstructive airways disease. The criteria for inclusion of patients in the study were suffi-

TABLE 3.—Data from Selected Studies Showing the Decline of Certain Pulmonary Function Variables in Patients with Obstructive Lung Disease and in Normal Subjects

<i>Study</i>	<i>Test*</i>	<i>Change (ml/year)</i>
Chronic obstructive lung disease		
Howard (34)	FEV _{0.75}	-83
Fletcher and Oldham (35)	VC	-79
Burrows and Earle (33)	VC	-86
	FEV _{1.0}	-56
Normal subjects		
Kory et al. (36)		
Men	VC	-22
	FEV _{1.0}	-28
Ferris et al. (37)		
Men	FVC	-25
	FEV _{1.0}	-27
Women	FVC	-23
	FEV _{1.0}	-22

*Abbreviations: VC = vital capacity; FVC = forced vital capacity; FEV = forced expiratory volume (subscript refers to time of measurement in seconds).

ciently rigid that only patients with advanced disease were enrolled; however, data on them are by no means unique, as is shown in Table 3 in which the results of somewhat similar studies by English investigators are presented.³⁴⁻³⁶ In England the deterioration of FEV₁ per year was even greater than that observed in the United States study. All of these values are several times greater than the normal attrition of FEV₁ that occurs with age, as was documented by the large surveys of Kory et al.³⁶ and Ferris et al.³⁷

There were some interesting trends evident in the British studies that pertain to the question of prevention and therapy. Howard³⁴ observed that patients who smoke heavily have a greater worsening of their ventilatory capacity than those who have either stopped smoking or continued at a reduced rate. Similarly, he observed that the deterioration is accelerated in those patients who have more frequent respiratory infections as documented by the number of courses of antibiotics required in a given period. In a report to the British Medical Research Council Fletcher and Oldham³⁵ further evaluated antibiotics in patients with chronic bronchitis and found that antibiotics do not significantly reduce the number of intercurrent respiratory infections, but serve to reduce the number of days of disability from them. This finding is consistent with the current belief that intercurrent infections, which plague the life of patients with chronic obstructive lung disease, are initiated by nonbacterial

TABLE 4.—General Categories of Treatment That Are Frequently Administered to Patients with Chronic Obstructive Lung Disease

<i>Category of Treatment and Methods</i>
A. Prevent inflammation
1. Stop smoking
2. Treat infection
3. Avoid pollutants
B. Expectorants
1. Hydration
2. Pharmaceuticals
C. Bronchodilators
1. Catecholamines
2. Theophyllines
3. Steroids
4. Other
D. Ventilatory support
1. Oxygen
2. Mechanical ventilation
E. Rehabilitation

agents (presumably viruses) but are then perpetuated and aggravated by secondary bacterial superinfection of the lower airways.

Table 4 lists the general categories of treatment that have been used for patients with chronic obstructive lung diseases. One must appreciate the difficulties in evaluating the influence of a single therapeutic approach when it is given to a group of patients with a disease that characteristically waxes and wanes who are usually treated with multiple remedies. But in all studies in which the effects of bronchodilators, expectorants, antibiotics, oxygen, and rehabilitation were examined, one uniformly finds that there is *never* an improvement in pulmonary function; in fact there is a steady reduction in FEV₁. The sad conclusion emerges that despite all known therapeutic interventions tried to date, nothing has been found that will retard, much less reverse, the relentless tendency for the obstruction of airways to increase.

On the brighter side, however, is the reasonably consistent subjective improvement felt by patients in various rehabilitation programs. The patients feel better, they have greater independence in their daily activities, and they seem to enjoy life more. Also, one can show an increase in their work capacity, which in view of the lack of change in pulmonary function is generally attributed to the effects of training and physical conditioning. Finally, one important benefit from

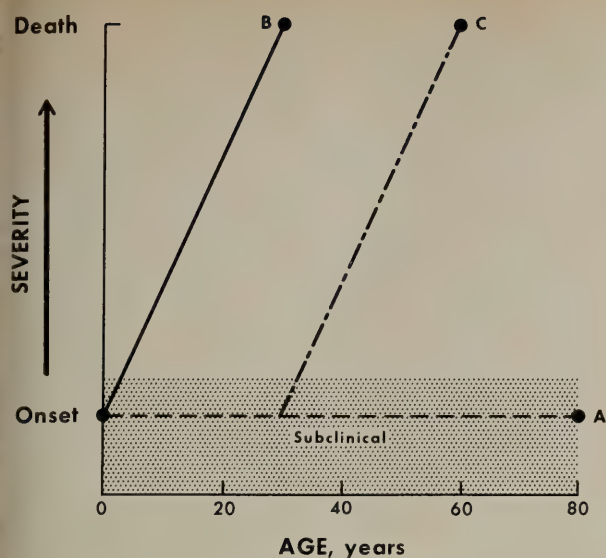


Chart 9.—A schematic representation of three possible clinical courses that a patient with a genetic abnormality could follow. (Line A = no detectable disease; line B = continuously progressive disease leading to death; and line C = disorder without clinical manifestations unless external factors are introduced.)

the various therapeutic interventions is that they keep the patient out of the hospital, so there is a definite socio-economic gain from treatment. It should be emphasized that the rather gloomy conclusions concerning the effects of treatment on pulmonary function were obtained in studies of patients with *advanced* pulmonary emphysema and bronchitis. The results of treatment in the patient with very early disease, or in those predisposed to the development of chronic obstructive lung disease, are unknown and will depend to a large extent on the mechanisms by which progressive loss of pulmonary function occurs.

Chart 9 shows some possible clinical courses that a person with a genetic abnormality might follow during the (possible) development of his disease. There are a number of permutations on the pathways that are shown, but the three indicated in the chart serve well as prototypes for discussion. The figure depicts the increasing severity of a given disease from its onset to the patient's death. The time scale is in years to represent an arbitrary selection of the duration of the illnesses. Line A indicates the subject who has a specific genetic abnormality but one which is completely harmless and not associated with clinically detectable disease. An example of this might be the person who has beta-aminoisobu-

teric aciduria, an easily identified, genetically determined, biochemical abnormality of renal function that, as far as we can tell today, has absolutely no clinical consequences. In contrast, Line B depicts a genetic abnormality that causes inexorably progressive disease leading to the death of the patient. Examples of genetically determined diseases that follow the course shown by Line B and are usually lethal in adulthood are some of the lipidoses and hemoglobinopathies. Line C represents the course of a patient who has a genetic abnormality that, by itself, would be inconsequential and would probably never be detected unless external factors are introduced and make the deficiency evident. The classic example of this kind of abnormality is the person with glucose-6-phosphate dehydrogenase deficiency. Unless an afflicted person eats fava beans or is given various antimalarial drugs or other agents that induce a severe hemolytic reaction, he is completely asymptomatic and his genetic liability will probably remain undiscovered all his life.

Dr. Cohen has already indicated that the clinical course of the patient with genetically induced deficiency of ALT is unknown at present. Some investigators believe that patients with heterozygous deficiency follow Line A and that they are not predisposed to the development of obstructive lung disease.³⁸ Others believe that patients with homozygous deficiency follow Line B and hence are predisposed to the development of extensive destructive lung disease at an early age.³⁹ Another opinion, based primarily on the studies by Kueppers, Fallat, and Larson²⁶ and Lieberman and coworkers,²⁷ is that the pathway for *both* homozygotes and heterozygotes is that depicted by Line C. The genetic predisposition confers a vulnerability for the development of lung disease but external factors are presumably necessary to initiate the series of events that results in destruction of lung tissue. This is an important concept because, if subsequently proved, it underscores the importance of therapy directed at control of the external factors.

Of the conventional forms of treatment shown in Table 4, those that appear to be most valuable in the treatment of early (asymptomatic) chronic obstructive lung disease are directed toward the prevention of inflammation and the control of infection. Bronchodilators, expectorants, and the other remedies are *ex post facto*, since our

aim is to arrest the disease in its early stages before these remedies will be applicable. Prevention of inflammation and control of infection are applicable to both patients with $\Delta 1\text{T}$ deficiency and patients with early emphysema or chronic bronchitis without a detectable biochemical abnormality because there is reason to believe that infection and inflammation of the airways and lung parenchyma are critically related to the progressive loss of pulmonary function.

It is mandatory that patients avoid all forms of tobacco. Smoking seems to be clearly the most important cause of widespread pulmonary inflammation, and cessation is probably the single most important preventive maneuver one can offer. The role of pollution from environmental sources has been difficult to characterize owing to its numerous complexities, but available evidence indicates that it does aggravate pulmonary function disturbances in patients who have underlying lung disease and that it can cause pulmonary inflammatory reactions. Therefore, air pollution could either initiate or compound a series of events that would culminate in more advanced lung disease.

Intercurrent lower respiratory tract infections are a frequent and troublesome problem in patients with asthma, chronic bronchitis, and emphysema. Respiratory infections are more prominent in these patients in the late stages of their illness, but careful questioning often reveals that unusually frequent and troublesome (compared with normal persons) "colds" or episodes of "bronchitis" have been present for many years or even decades. Whether or not patients with $\Delta 1\text{T}$ deficiency are prone to frequent development of pulmonary infections has not been definitely established. However, all patients with documented early obstructive lung disease and those persons with biochemical abnormalities that may predispose to lung disease should be cautioned about the need for prompt and vigorous treatment of all infections of the lower respiratory tract. The earliest symptoms and signs of these infections are cough and the production of purulent sputum. Fever, leukocytosis, and changes detectable on chest roentgenograms are nearly always absent for the first several days and often are absent for the duration of the illness. Even though it is usually difficult to isolate a "pathogen" on sputum culture, cough and sputum production in these patients usually respond prompt-

ly to the administration of either tetracycline or ampicillin, especially if it is given early. It is possible that in the next few years additional antiviral agents, such as amantadine, will be available for the treatment of antecedent viral respiratory infections that seem to predispose to subsequent bacterial superinfection.

I should emphasize that these recommendations are based on unproved assumptions and that they are made from an optimistic viewpoint. We now have available diagnostic techniques that permit us to identify those patients with $\Delta 1\text{T}$ deficiency that is associated with a high incidence of pulmonary emphysema and to detect by means of easily performed pulmonary function studies evidence of either breakdown of lung tissue or disease of small airways in asymptomatic patients. A preventive regimen comparable to that just outlined offers the best hope of inhibiting or arresting the disease process. We may hope that as additional patients with early disease or predisposing abnormalities are discovered and followed over the next several years, additional information will be discovered that can be used to control the epidemic of advanced and poorly treatable chronic obstructive lung diseases.

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CONCEALED POSTPARTUM HEMORRHAGE

A very serious postpartum hemorrhage that one may have to deal with and *can* deal with very effectively is the concealed hemorrhage, usually high in the vagina above the site of episiotomy. Typically one has delivered the baby, has perhaps repaired an extended episiotomy, gone home, and an hour later the patient (without any external bleeding) is in shock. The physician goes back to find a concealed hemorrhage high in the vagina. He can actually feel this rectally and vaginally. . . .

We have a method of treating this that I very much recommend. That is to open the episiotomy wide and attempt to evacuate. This is where suction would be helpful. Evacuate as much of this clot as you can. If you do not it will dissect all the way up retroperitoneally. Almost universally you will not find bleeding areas. At this point take a gall bladder drainage tube, one cut off so that it's just at the base of the cavity where you evacuate the hemorrhage; and bring it out of the buttocks and through the ischiorectal fat. Tie it with a suture to the skin and close that episiotomy tightly. They heal by primary intention. One actually has drainage through this. It may stay in about ten days. One actually can get out of what could be a very serious complication with a very nice result.

Needless to say the vagina is then packed tightly with as much gauze as you can use, and of course an indwelling catheter would be necessary. That pack is left in for 24 hours and blood is replaced.

—ISADORE DYER, M.D., New Orleans
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Correction

Immunological Mechanisms of Glomerulonephritis

In the printing of the Medical Staff Conference on Immunological Mechanisms of Glomerulonephritis, published in the January 1972 issue of this journal, a considerable portion of the discussion by Curtis B. Wilson, M.D., was inadvertently omitted.

The point at which the material was omitted was on page 50, column 2, line 24, between "circulating anti-thyroglobulin" and "may help explain these observations."

Printed below are the paragraphs as they should have appeared:

Thyroglobulin anti-thyroglobulin immune complex nephritis has been produced experimentally, and at least two cases have occurred in humans. The possibility of precipitating nephritis in a thyroiditis patient who has circulating anti-thyroglobulin antibodies should be considered when therapeutic procedures might shift the antigen-antibody balance toward slight antigen excess with the potential of forming soluble nephrotoxic complexes.

The experimental nephritis produced originally by Heymann in rats by repeated injections of rat kidney in adjuvant has been shown to be an immune complex nephritis in which the antigen originates in the apex of the proximal convoluted tubular cell of the nephron and is also present in the circulation.²¹ This model of nephritis might have significance in some of the cases of recurrent glomerulonephritis seen after transplantation.

In summary, however, most antigens in immune complex induced nephritis remain unknown.

Another form of probable immune complex glomerulonephritis is seen most commonly in

hypocomplementemic children and is characterized by heavy granular deposits of C3 along the GBM with or without immunoglobulin in the same distribution.²² When studied serially, the immunoglobulin, if present, may disappear with time while C3 remains.²³ Little is known about the relative disappearance rates of immunoglobulin and complement from glomerulonephritic kidneys; however, serial observations in patients with immune complex nephritis and rabbits with serum sickness indicate that C3 persists after immunoglobulin becomes undetectable. In our own adult series of patients, we have found that five to ten percent of biopsies contain granular glomerular C3 deposits without immunoglobulin. The recent description of the serum C3 proactivator by Götze and Müller-Eberhard may help explain these observations.²⁴ This 5S pseudoglobulin of β mobility and 80,000 molecular weight possesses C3 convertase activity when activated by another, probably enzymatic, serum component and results in C3-9 consumption. Biologically active complement products, namely anaphylatoxins and chemotactic factors, may be generated by this mechanism without involving the classical C1,4,2 pathway.

MEDICAL STAFF CONFERENCE

Manifestations and Treatment of Acromegaly

These discussions are selected from the weekly staff conferences in the Department of Medicine, University of California, San Francisco. Taken from transcriptions, they are prepared by Drs. Sydney E. Salmon and Robert W. Schrier, Assistant Professors of Medicine, under the direction of Dr. Lloyd H. Smith, Jr., Professor of Medicine and Chairman of the Department of Medicine. Requests for reprints should be sent to the Department of Medicine, University of California, San Francisco, San Francisco, Ca. 94122.

DR. SMITH:* We are very fortunate to have Dr. Seymour Levin with us today to discuss the manifestations and treatment of acromegaly.

DR. LEVIN:† It has been 85 years since Marie's¹ description of acromegaly and 45 years since Davidoff's² detailed review of the clinical findings in 100 patients seen at the Peter Bent Brigham Hospital from 1913 to 1926. Davidoff's study remains one of the most valuable analyses of the disease though published in an age in which treatment of this condition was just beginning. I would like to review with you some of our clinical findings and compare them with those of Davidoff. In addition, I will discuss metabolic studies in 50 patients before and after cryohypophysectomy, the major form of treatment now used at the University of California, San Francisco.

Acromegaly is a disease which is the result of the chronic effects of excessive pituitary growth hormone (somatotropin) secreted during adult life. It is of interest that the Davidoff studies, and collaborative surgical and pathological studies with Harvey Cushing, were done at the same time growth-producing properties of the pituitary were being discovered at this school by

Evans and Long.³ Table 1 compares the clinical data in Davidoff's patients with those in our series. The sex distribution and age are surprisingly similar. The shorter duration of symptoms in our patients is probably the result of earlier detection today.

Symptoms

The symptoms reported in the two series are shown in Table 2, arranged according to the time sequence of appearance. The earliest symptoms are of a nonspecific nature. Cosmetic changes are often apparent to others, but not to the patient until later. The more frequent occurrence of sexual dysfunction in the Davidoff series, as compared with our study, is probably related to longer duration of the disease in their patients.

Paresthesias are an early symptom and may result initially from metabolic effects of growth hormone upon the nerves⁴ rather than from an entrapment of the median nerve (carpal tunnel syndrome) which occurs later in the illness. Figure 1 shows a patient at 25 years of age. At that time she noted some tingling of her hands, but did not see a physician. Her features, however, were suggestive of very early acromegaly. Over the years she experienced fatigue; but it wasn't until six months ago, at the age of 46

*Lloyd H. Smith, Jr., M.D., Professor and Chairman, Department of Medicine.

†Seymour R. Levin, M.D., Assistant Research Physician, Metabolic Research Unit.

TABLE 1.—Clinical Review of Acromegaly

	Davidoff (1926)	Present Study (1971)
Number of Patients	100	50
Sex	44% M, 56% F	50% M, 50% F
Mean Age	Slightly over 40 years	42 (21 - 65) years
Duration of Symptoms	About 15 years	9.6 years

TABLE 2.—Symptoms in Acromegaly

	Davidoff (1926)	Present (1971)
<i>Earliest</i>		
Fatigue or Lethargy ...	42%	82%
Paresthesias	30%	62%
Amenorrhea	73% of females	32% of females
Headache	87%	64%
<i>Later</i>		
Excessive Perspiration ..	60%	88%
Weight Gain	39%	76%
Photophobia	12%	46%
Acral Enlargement	100%	96%
Voice Change	?	50%
Decreased Libido	38%	27%
<i>Late</i>		
Joint Pain	?	76%
Cardiac Symptoms	?	12%

TABLE 3.—Signs in Acromegaly

	Davidoff (1926)	Present (1971)
Acral Changes	100%	96%
The Warm, Moist, Fleshy, Handshake	?	96%
Hypertension	?	23%
Goiter	25%	18%
Lactation	4%	8%
<i>Dermal Changes</i>		
Fibromata Mollusca	27%	38%
Acanthosis Nigricans	?	26%

(Figure 1), that her headache became so severe that she sought help, and the diagnosis of acromegaly was made. Besides cosmetic deformity, she was found to have suprasellar extension of the pituitary tumor, glucose intolerance, early heart failure, lactation, and hypertrophic arthritis. Earlier detection and treatment might have avoided this extreme progression of the disease.



Figure 1.—Patient at age 25 with very early symptoms, and at age 46 with late symptoms and signs of acromegaly.

Physical Signs

The physical signs of acromegaly were quite similar in the two series (Table 3). However, Davidoff did not mention the warm, moist, fleshy handshake, reflecting hypermetabolism and increased soft tissue mass, which we consider so characteristic of acromegaly.

Lactation was present in two males and two postmenopausal females in our series. Lactation may occur in many types of pituitary disorders.⁵ It is often not noted by the patient and requires proper examination by the physician to extrude some milk. A gentle, para-areolar pressure is followed by a symmetrical, firm rolling movement of the nipple with the sides of the thumbs (Figure 2). Large tumors which have been present for a long time appear most likely to be associated with the presence of lactation. Inhibition of prolactin inhibitory factor (PIF) in the hypophyseal stalk is probably responsible for lactation in patients with pituitary tumors. Reduced secretion of PIF is thought to allow for the release of pituitary prolactin and subsequent lactation. In addition, growth hormone itself may have some lactogenic effects.^{6,7}

Of the skin changes, acanthosis nigricans has been of interest to us, since we have seen it in six of our last 23 patients. Microscopic skin folding and increased pigment produce a dark, carpet-like texture to the skin in the axillae (Figure 3). It may provide an important clue to the existence of acromegaly, as well as other pituitary tumors.⁸ Controversy exists as to whether in acromegaly the lesion should be called "pseudo"-acanthosis nigricans, a condition which occurs in areas of excessive sweating and pressure and is identical histologically with true acanthosis ni-

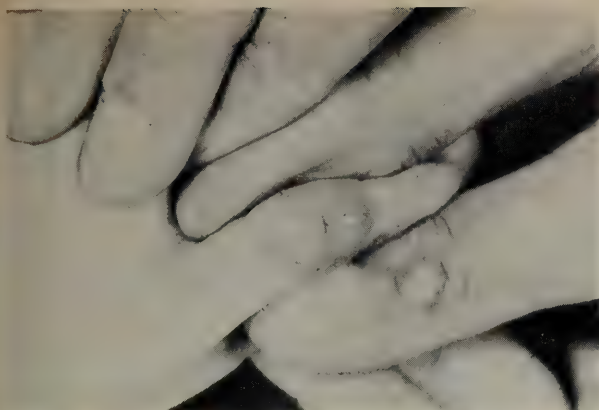


Figure 2.—Demonstration of galactorrhea by gentle extrusion of milk, using a rolling motion with the thumbs.

gricans. We have, however, seen this skin lesion in patients with acromegaly who were not sweating excessively and did not have thickened skin.

Radiological Signs

Davidoff² reported radiographic demonstration of an enlarged sella turcica in 93 percent of his patients, while we have seen this condition in 90 percent of our patients. This finding is often accompanied by enlarged frontal sinuses, hyperostosis frontalis, and enlarged mandible (Figure 4). Most of these changes are the result of remodeling of bone due to proliferative changes in cartilage.

Soft tissue thickening of the hands and an enlarged sesamoid bone (Figure 4) are frequently present. An increased sesamoid index,⁹ that is, greatest longitudinal diameter times greatest horizontal diameter of the thumb sesamoid bone (upper limit of normal is 29 mm), is probably not as reliable a sign as is the heel pad thickness. Steinbach¹⁰ reported eight years ago that the best radiological sign is a thickened heel pad. This is the shortest vertical distance from the calcaneus to the volar surface of the foot (Figure 4). Ninety-eight percent of our patients have heel pad thickness over 22 mm, which is considered the upper limits of normal.

All of our patients had pneumoencephalography (PEG) to delineate the upper limits of the pituitary gland. A recently appreciated radiological finding is the "empty sella syndrome"^{11,12} which was seen with the PEG in 8 percent of our patients. This condition represents an abnormal extension of the subarachnoid space downward into the sella, so that air introduced during the



Figure 3.—Acanthosis nigricans in a patient with acromegaly.

PEG extends into this space (Figure 5). Thus, the sella is not really empty, but is occupied by the pituitary gland and subarachnoid space. Many conditions, including perfectly normal endocrine states may be associated with an "empty sella."¹³ The incidence of subarachnoid space observed extending into the sella radiologically in our series is less than that seen anatomically in a random autopsied population;¹⁴ thus this finding has no specificity for acromegaly.

Laboratory Studies

While physical symptoms and signs and radiological findings are helpful, the definitive diagnosis of acromegaly is best made in the laboratory. The finding of an increased level of the fasting human growth hormone (HGH), which is not suppressible by glucose,¹⁵ is the most definitive means of diagnosing acromegaly. We therefore measure HGH both after fasting and one hour after 100 gm of oral glucose. Acromegalic patients have HGH which is usually above 10 m μ g per ml and does not suppress after glucose. In 20 percent of our patients a rise in HGH was seen after oral glucose. Non-acromegalic subjects, especially premenopausal women, may have elevations of HGH above the normal value of 5 m μ g per ml with stress, prolonged fasting, anxiety or exercise; but one hour after ingestion of 100 grams of glucose, HGH decreases to less than 1 m μ g per ml. The elevation of fasting HGH and its non-suppressibility by glucose may result from the secretion of excessive hypothalamic growth hormone releasing factor (GHRF), although this factor has not yet been measured directly.¹⁶

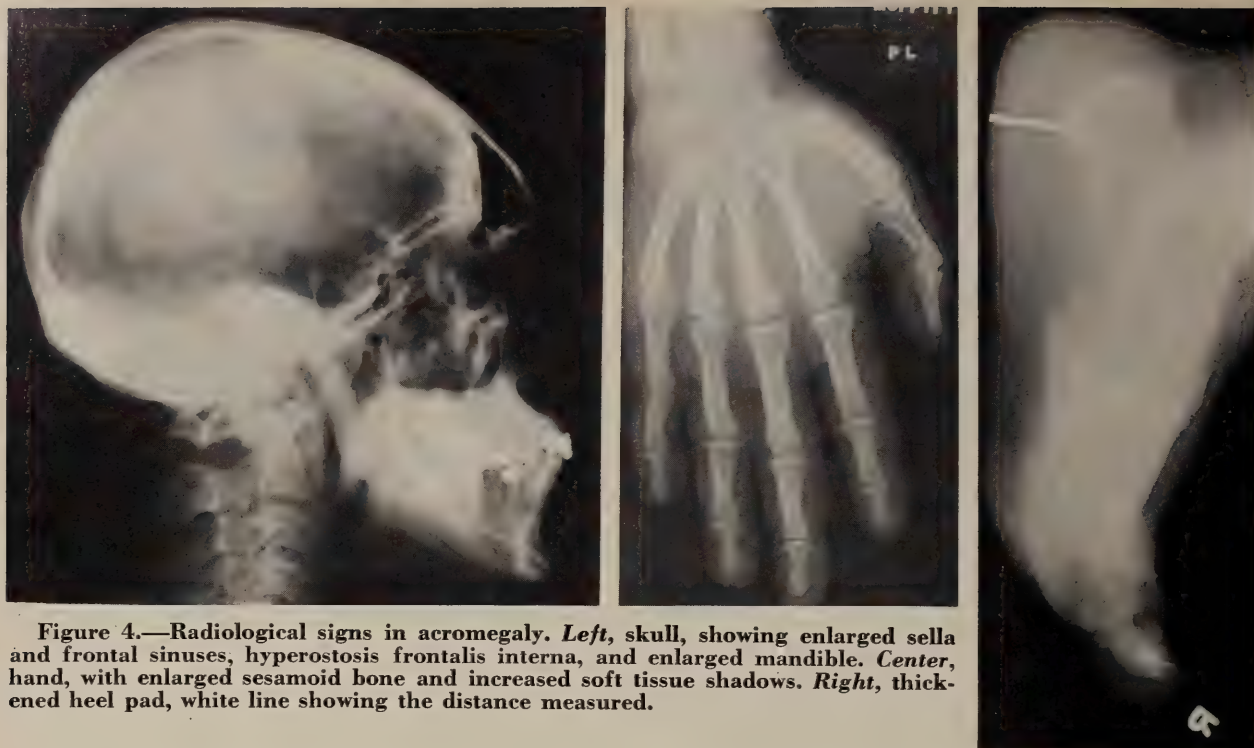


Figure 4.—Radiological signs in acromegaly. *Left*, skull, showing enlarged sella and frontal sinuses, hyperostosis frontalis interna, and enlarged mandible. *Center*, hand, with enlarged sesamoid bone and increased soft tissue shadows. *Right*, thickened heel pad, white line showing the distance measured.

The diurnal pattern of HGH secretion in normal subjects and in acromegalic patients is strikingly different.¹⁷⁻²⁰ Normally, morning values are less than 5 m μ g per ml in the recumbent, fasting state, and there is an early fall after meals. Three to four hours after meals there may often be a small rise in HGH (3 to 8 m μ g per ml) in ambulatory subjects. At night, 45 to 90 minutes after falling asleep, normal subjects have a considerable rise in HGH which is often as high as 10 to 35 m μ g per ml. The peak level occurs when the

electroencephalogram (EEG) sleep pattern is associated with nonrapid eye movements, and this level of HGH can be altered by changing sleep cycles.²¹

In contrast to normal subjects, the acromegalic patient has high HGH levels which do not vary consistently with meals or sleep. This chronic, nonrhythmic secretion of high levels of HGH results in the physical and metabolic changes characteristic of acromegaly.

The metabolic effects of HGH may occur only when the structure of the hormone is altered to form "sulfation factor".^{22,23} This factor, when exposed to rachitic rat cartilage *in vitro*, will increase the uptake of radioactive sulfur, thymidine,²⁴ and proline²⁵ by the tissues, thereby reflecting growth of cartilage. Unaltered HGH instilled directly into the cartilage preparation *in vitro* will not cause increased sulfur uptake.

In addition to measuring HGH after a glucose load, the glucose tolerance test and serum immunoreactive insulin provide excellent means of following the patient's acromegalic status with relationship to the effect on carbohydrate metabolism. Preoperatively, we have observed hyperinsulinism in 66 percent of our patients in the presence or absence of an abnormal glucose tolerance test. An effect of HGH as a peripheral insulin antagonist has been suggested and re-



Figure 5.—Pneumoencephalogram showing an "empty sella" in a patient with acromegaly. White arrows show air anterior and posterior to the pituitary gland.

lated to increased lipolysis and free fatty acid oxidation subsequently interfering with glycolytic pathways.^{23,26,27,28} Although direct insulinotropic actions of HGH have not been demonstrated *in vitro*, effects on insulin secretion may be involved in hyperinsulinism observed in acromegaly. When HGH levels are reduced, most patients have a concomitant improvement in glucose tolerance and lowering of insulin levels.

Assessment of adrenal and thyroid function should be undertaken in the acromegalic patient. To test adrenal function the metyrapone²⁹ and insulin hypoglycemia tests^{30,31} are useful. Thyroid function is evaluated using the total thyroxine levels, T₃ uptake, and radioactive iodine uptake. In most instances, thyroid and adrenal function are found to be normal in acromegaly.

Recently, in collaboration with Drs. A. Charro and S. Friedman, we have measured gonadotropin levels using radioimmune assays for luteinizing hormone (LH) and follicular stimulating hormone (FSH). Using clomiphene citrate, an inhibitor of estrogen activity which results in stimulation of hypothalamic releasing factors and subsequent pituitary gonadotropin secretion, we have studied LH and FSH in acromegaly.³² It had been thought formerly that in acromegaly gonadotropin secretion was deficient as a result of tumor expansion. Yet, in ten of twelve male patients with acromegaly and decreased libido the basal levels of LH and FSH were normal, and these levels increased normally during clomiphene administration. However, basal testosterone levels were low and response to increased endogenous gonadotropins was impaired. Thus, the gonadal testosterone response to gonadotropins, but not the gonadotropin levels, is reduced in acromegaly. The mechanism for this low testicular output of testosterone is unknown but may relate to an atypical structure of LH or FSH or both; or it is due to interference by HGH of testicular biosynthetic or secretory processes.

Occasionally other endocrine diseases are found with acromegaly. In our series of 50, we have seen four patients with thyroid nodules, two patients with hyperparathyroidism and one patient with Graves' disease.

Therapy

A recent mortality study of 194 patients by Wright et al³³ showed that after 45 years of age the annual death rate in patients with acro-

TABLE 4.—*Acromegaly Treatment Used Today*

1. Irradiation
 - a) Conventional Radiotherapy (34, 35, 36)
 - b) Implants: Yttrium⁹⁰, gold¹⁹⁸ (37)
 - c) Heavy particle; proton beam; alpha particle (38, 39)
2. Surgical
 - a) Craniotomy (40)
 - b) Transsphenoidal, direct vision (41)
 - c) Stereotaxic
 - 1) Cryosurgery (42, 43, 44)
 - 2) Radiofrequency (45)
 - 3) Ultrasonic (46)
3. Medical
 - a) Medroxyprogesterone (47, 48)
 - b) Chlorpromazine (49)

megaly was two to three times greater than in the normal population. Furthermore, the mortality rate was even greater in those patients with clinical diabetes. The most frequent causes of death were related to cardiovascular, cerebrovascular and respiratory diseases. The mortality rate in patients who had received some forms of treatment for acromegaly was less, thus documenting the need for treatment of this chronic disease.

The various forms of treatment are shown in Table 4 with accompanying references.³⁴⁻⁴⁹ The treatment used at the University of California, San Francisco, is cryohypophysectomy. Reduction in HGH levels is observed within a few days after cryosurgical treatment, whereas after radiation months or years may pass before low levels are attained. Metabolic responses to cryohypophysectomy are seen within a few weeks after operation.⁵⁰ Of the surgical approaches, the stereotaxic (that is, use of radiological guidance in performing the procedure) methods avoid craniotomy and extensive manipulation of brain tissue.

Experience with medroxyprogesterone as a medical means of reducing HGH has provided interesting new possibilities, but results have varied. The efficacy of chlorpromazine, an inhibitor of HGH responses in normal men (probably by acting upon hypothalamic pathways), remains to be evaluated in acromegaly.

Transsphenoidal cryohypophysectomy, as performed by Drs. John Adams and Robert Seymour of the University of California, San Francisco, Department of Neurosurgery, consists of the pas-

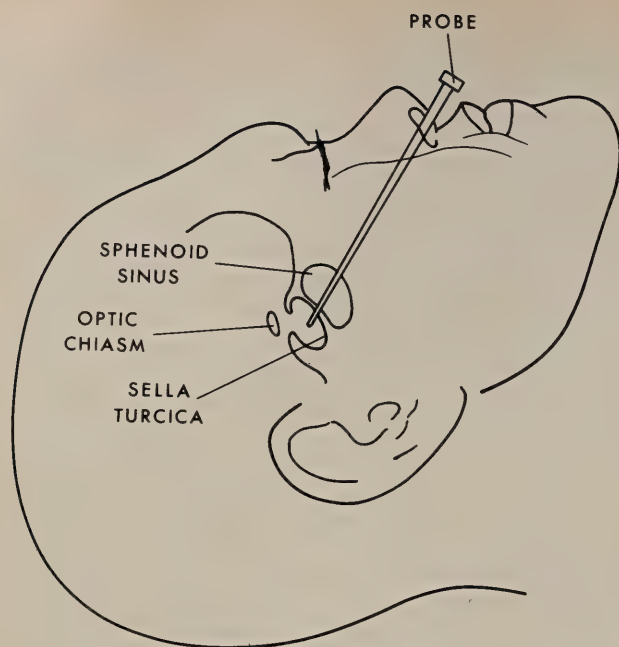


Figure 6.—Diagram of transsphenoidal surgical approach to pituitary gland with the cryohypophysectomy probe.

sage of a probe through the sphenoid sinus into the sella turcica (Figure 6) with subsequent placement of lesions in the pituitary by cold injury. This is done with lateral image intensifier and anterior-posterior polaroid x-ray guidance. Local anesthesia is used so that vision and eye movements can be evaluated throughout the procedure. Biopsy material also can be obtained through the probe. Pronounced suprasellar extension, as observed on pneumoencephalography, is a relative contra-indication to this form of surgical treatment, since cold injury might be conducted to the optic nerve.

Eighty-two percent of our 50 patients have been followed at least one year after operation. Drs. Nathan Becker, Fred Hofeldt and Victor Schneider collaborated in the evaluation of these patients who were in hospital at the General Clinical Research Center. Several endocrine and metabolic abnormalities may occur after treatment. During the first postoperative week there are alterations in water balance which are often predictable as to time and are triphasic in sequence. A diabetes insipidus syndrome occurred in one-third of our patients within the first 48 postoperative hours. This usually subsided; then during the fourth to sixth postoperative days hyponatremia occurred in one-fifth of the patients.⁵¹ This condition is associated with a posi-

tive water balance and is best treated by water restriction. The concentration of sodium in the urine may be normal or high, and the syndrome appears to be primarily related to an inappropriate secretion of antidiuretic hormone (ADH). In two of the 50 patients a clinical picture of diabetes insipidus, which could be treated with chlorpropamide,⁵² occurred on the eighth to tenth postoperative day. Thus, a triphasic sequence of altered water balance (consisting of an early ADH deficiency syndrome, then excessive release of ADH, and finally the late appearance of ADH deficiency) may occur after pituitary operation.⁵³ We have never observed all three phases to occur in the same patient. These changes have been described in humans after head injuries⁵⁴ and stalk sections⁵³ and in experimental animals after hypophysectomy.⁵⁵

Other short and long term complications of cryohypophysectomy for acromegaly are seen in Table 5. Of interest is the fact that the procedure appears to reduce the release of HGH without causing hypopituitarism in the majority (88 percent) of patients.

Beneficial effects may be observed as early as the first postoperative week, when the patient notes less bulk in hand and facial tissues. During the ensuing weeks and years many symptoms subside in association with the reduced level of HGH. We have considered optimal response to be a fall in HGH level to less than 10 m μ g per ml. We have correlated the extent of HGH changes with improvement of symptoms (Table 6). Most symptoms are improved to a greater degree in patients whose HGH levels decrease to less than 10 m μ g per ml after treatment. Improvement in some symptoms, such as fatigue, headache and arthralgias, could not, however, be correlated with the level of HGH. Reversal of cosmetic alterations can be expected to occur only in those cases which are diagnosed and treated early in the course of the disease. Although soft tissue enlargement can be reduced, bony and cartilaginous changes show only minimal improvement.

The mean fasting HGH before cryosurgical operation in our 50 patients was 52 m μ g per ml. Postoperatively, at most recent follow-up examinations (eight patients at six weeks, 17 patients at one year, 11 patients at two years, 11 patients at three years, three patients at four years), the mean fasting HGH was 16.8 m μ g per ml. The majority of patients (76 percent) have postoperative

TABLE 5.—Complications of Cryohypophysectomy

Incidence/Total Patients

First 10 postoperative days

Diabetes insipidus	10/50	} Transient
Hyponatremia	5/26	
Optic problems	9/50*	
CSF rhinorrhea	3/50	
Meningitis	2/50 (D. pneumonia)	
Deaths	None	

Late postoperative period (over 6 weeks)

Adrenal insufficiency	6/50
Hypothyroidism	5/50
Diabetes Insipidus	2/50

*7 patients with paralysis of extraocular muscles, 2 patients with visual field defects.

HGH less than 10 μg per ml. Before operation 44 percent of the patients had an abnormal oral glucose tolerance test, while 8 percent had overt clinical diabetes. At our recent follow-up examination after operation only 28 percent of the patients had an abnormal glucose tolerance test, but all 8 percent still had overt clinical diabetes, although milder than it was preoperatively. The incidence of hyperinsulinemia was reduced in most patients as well.⁵⁶

In summary, the classical appearance of a patient with far-advanced acromegaly makes the diagnosis easy. The challenge to physicians, however, is to detect and treat the disease before cosmetic, metabolic, and vascular changes are far advanced. Using a practical and precise method of measuring HGH before and after a glucose load allows such early detection of the disease.

Cryohypophysectomy is a form of treatment which alters the metabolic derangements in acromegaly, often without interfering with other pituitary functions.⁵⁷ At present this procedure appears to be a rapid, safe, and effective means of lowering HGH levels and thereby improving or preventing many of the clinical and metabolic disorders observed in acromegaly.

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TABLE 6.—Relationship of Alteration of Symptoms to Postoperative Growth Hormone Level*

Postoperative HGH ($\mu\text{g}/\text{ml}$)

	<10 $\mu\text{g}/\text{ml}$	>10 $\mu\text{g}/\text{ml}$
Acral Changes	53%	33%
Excessive Perspiration	72%	58%
Decreased Libido	33%	0%
Amenorrhea	29%	0%
Photophobia	31%	0%
Fatigue	33%	33%
Headaches	50%	55%
Arthralgias	56%	55%

*Values indicates percentage of patients with particular symptom that improved following cryohypophysectomy.

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THE OPHTHALMOLOGIST IN DIABETES

When do you think we as internists should send our diabetic patients to an ophthalmologist for evaluation?

I think that any patient who shows diabetic retinopathy of any extent should be sent to an ophthalmologist for complete evaluation of the fundus. If the internist who is following the patient for the diabetes is not accustomed to dilating the pupil once in a while for a fairly complete evaluation of the fundus, then I think that any person who has had diabetes for 10 years or longer, regardless of whether anything is seen in the fundus, should be sent to an ophthalmologist. A patient who is developing other complications, other vascular complications from their diabetes, either nephropathy or neuropathy, deserves a very thorough evaluation of the fundus. I think this is more important today than ever because we now realize that there is something that can be done for these people if they are seen early enough. Although we don't understand the exact mechanism of the pathogenesis, we do know enough about the evolution of the disease process to know that if it can be blocked at certain stages, the horrors that we see can sometimes be prevented. So in answer to the question once again, any patient who shows any degree of diabetic retinopathy should be evaluated by an ophthalmologist.

—EDWARD OKUN, M.D., St. Louis
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programs. For subscription information: 1930 Wilshire Blvd.,
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Important Advances in Clinical Medicine

Epitomes of Progress -- General Surgery

The Scientific Board of the California Medical Association presents the following inventory of items of progress in General Surgery. Each item, in the judgment of a panel of knowledgeable physicians, has recently become reasonably firmly established, both as to scientific fact and important clinical significance. The items are presented in simple epitome and an authoritative reference, both to the item itself and to the subject as a whole, is generally given for those who may be unfamiliar with a particular item. The purpose is to assist the busy practitioner, student, research worker or scholar to stay abreast of these items of progress in General Surgery which have recently achieved a substantial degree of authoritative acceptance, whether in his own field of special interest or another.

The items of progress listed below were selected by the Advisory Panel to the Section on General Surgery of the California Medical Association and the summaries were prepared under its direction.

Reprint requests to: Division of Scientific and Educational Activities, 693 Sutter Street, San Francisco, Ca. 94102

Selective Gastric Vagotomy

VAGOTOMY is well established in the surgical treatment of duodenal ulcer disease, but controversy continues as to whether the vagotomy should be truncal or selective and whether it should be accompanied by antrectomy or pyloroplasty. While no clearly significant differences in postoperative sequelae have been shown between truncal and selective vagotomy, there is evidence suggesting that the gastric denervation as judged by the Hollander test is more complete after the selective operation. This may

be due to the more demanding technique involved in selective vagotomy or may relate to some metabolic factor such as inadequate release of secretin by the duodenum in the presence of parasympathetic denervation—secretin being a potent inhibitor of gastrin stimulated gastric secretion.

While vagotomy with pyloroplasty has a slightly lower operative mortality rate, it is generally conceded to have a somewhat higher incidence of ulcer recurrence than vagotomy accompanied by antrectomy. The preliminary results of a prospective randomized study by Sawyers and Scott suggest that the ulcer recurrence rate is the same when selective vagotomy is used. Care must be taken to insure that the adequate antral drainage is obtained when pyloroplasty is used. The accumulating evidence

suggests that selective gastric vagotomy either with antrectomy or pyloroplasty may become increasingly important in the elective surgical treatment of duodenal ulcer for those accustomed to the technique. This should not detract from the well-established value of truncal vagotomy particularly when operation is performed under emergency circumstances.

DAVID B. HINSHAW, M.D.

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Antibacterial Agents to Control Infection Associated with Burns

INFECTION STILL IS THE PRIMARY cause of death in patients with extensive burns. Great strides have been made during the past decade in the topical and systemic use of antibacterial agents to treat burned patients. Antibacterials commonly used topically include mafenide (Sulfamylon®), silver nitrate, gentamicin and silver sulfadiazine. Topical agents serve only to treat burn wound sepsis and not other sources of infection such as pneumonia, phlebitis, and the urinary tract. These later infections require systemic antibiotic administration. Gentamicin and Sulfamylon used topically are effective clinically because they actively penetrate the burn wound in reasonable concentrations. Silver nitrate penetrates less well and hence is less helpful in established infections. Sulfamylon, silver nitrate, and silver sulfadiazine are effective against Gram-negative bacteria while gentamicin is equally effective against Gram-positive and Gram-negative organisms.

EARL F. WOLFMAN, JR., M.D.

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Intestinal Bypass for Morbid Obesity

ACCUMULATING EVIDENCE indicates that intestinal bypass procedures may be recommended for carefully selected massively obese patients who are unable to control their obesity problem by more conservative means. Scott et al have proposed that the bypass be accomplished by dividing the jejunum a few inches distal to the Treitz ligament and the ileum a few inches proximal to the ileocecal valve with end-to-end anastomosis of these segments. The open distal jejunum is drained by anastomosis with the transverse colon while the proximal jejunum is closed. Preliminary experience suggests that this arrangement relieves the tendency for ileal reflux frequently seen in the end-to-side type bypass introduced by Payne and DeWind. Eleven of the 12 patients in Scott's preliminary group lost weight at a satisfactory rate and had minimal problems with diarrhea. In addition there was a consistent associated reduction in the serum lipids.

The majority of these patients have significant fat accumulation in the liver before the operation, as well as other metabolic disturbances. The necessity for careful preoperative preparation and strict selection of patients must be emphasized, and close postoperative care and follow-up are essential.

DAVID B. HINSHAW, M.D.

REFERENCES

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Payne JH, DeWind LT: Surgical treatment of obesity. *Am J Surg* 118:141, Aug 1969

Mediastinoscopy in Patients with Cancer of the Lung

EXPLORATION OF THE MEDIASTINUM has found a place in the evaluation of patients with carcinoma of the lung. Mediastinoscopy via the midline suprasternal route under general of local

anesthesia has proved to be the most popular approach for this kind of exploration, although limited parasternal mediastinotomy has also been utilized safely and successfully. Lymph nodes in the paratracheal and subcarinal regions may be visualized and biopsy specimens taken during mediastinoscopy. Although the procedure is potentially hazardous, mortality in a series of 9,543 cases collected by Ashbaugh was 0.09 percent and morbidity was 1.5 percent.

Mediastinoscopy does not replace other diagnostic procedures in evaluating patients with cancer of the lung. It is most useful in patients with proximal lesions in whom resectability is in doubt and least useful in patients with asymptomatic peripheral lesions. Ipsilateral positive lymph node biopsy via the mediastinoscope does not necessarily mean that the cancer is incurable, since some patients with positive mediastinal lymph nodes survive five years following pulmonary resection for carcinoma of the lung.

This is a procedure which should be part of the armamentarium of every thoracic surgeon.

JAMES B. D. MARK, M.D.

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Morton JR, Guinn GA: Mediastinoscopy using local anesthesia. Am J Surg 122:696-698, Nov 1971

Aggressive Approach to Diagnosis of Lung Infiltrates in the Compromised Host

X-RAY SIGNS OF LUNG DISEASE in patients with impaired resistance to infection are frequently nonspecific and may be due to either their underlying disease or infection. Corticosteroids and cytotoxic drugs alter the inflammatory response and may prevent "classical" radiological features associated with many infectious agents. The life-threatening nature of infection and the extensive differential diagnosis of lung infiltrates and cavitation in these patients are so great as

to preclude other than an aggressive approach to identify the etiology. Sputum, preferably obtained by transtracheal aspiration, should be cultured for anaerobic, and aerobic bacteria, mycobacteria and fungi; within a brief period acid fast, silver (for pneumocystis and fungi) and Gram stains should be performed. If stains are unrevealing, the patient's condition and the severity of his lung disease should dictate the necessity of either closed lung aspiration or biopsy. If either is performed, and immediate staining does not reveal a cause, open lung biopsy should be carried out.

JACK S. REMINGTON, M.D.

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Johnson HD, Johnson WW: Pneumocystis carinii pneumonia in children with cancer—Diagnosis and treatment. JAMA 214:1067-1073, Nov 9, 1970

Lymphocyte Tissue Culture in Transplant Surgery

THE *in vitro* RESPONSIVENESS of lymphocytes taken from transplant recipients has been the subject of a number of contradictory reports: to some extent this reflects various pitfalls in the quantitation of lymphocyte cultures, especially in a complex clinical situation. Nevertheless, it is the overall impression that when a satisfactory level of immunosuppression has been reached, the transplant patient's lymphocytes have a reduced response to phytohemagglutinin, and that a return to a normal responsiveness frequently heralds a rejection crisis.

Preceding rejection episodes there also appears to be an increased traffic in the blood of activated lymphocytes similar to that associated with vaccination or virus infection; this is reflected in an increased rate of spontaneous transformation in leukocyte cultures. The presence of activated cells in the circulation may also be detected either by counting atypical mononuclears in the peripheral blood, or by measuring the increased rate of RNA synthesis in very short-

term culture. Unlike most of the other techniques, these latter two approaches have the merit of giving relatively prompt answers, a *sine qua non* in the clinical management of this class of patient.

ALAN S. COULSON, M.A., M.B., PH.D.
ROY COHN, M.D.

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Coulson AS, Inman DR: Current clinical applications of lymphocyte tissue culture. *Guy's Hospital Reports* 1971, in press

The Role of Parathyroidectomy in Secondary Hyperparathyroidism

INCREASED PARATHYROID ACTIVITY has long been recognized as a common feature of advanced renal disease. As the lives of the patients are being prolonged by improved conservative therapy, by hemodialysis and by transplantation, the complications of overt hyperparathyroidism are being encountered with increasing frequency.

Because of the altered renal function, the usual biochemical determinations that are so important in the diagnosis of primary hyperparathyroidism are of limited value in detecting secondary hyperparathyroidism. One or more of the following manifestations may be present: (1) radiographic and clinical evidence of osteodystrophy, (2) soft tissue calcifications, (3) intractable pruritus, and (4) persistent and symptomatic hypercalcemia.

The majority of patients with these complications will respond to vitamin D along with measures to lower the serum phosphate level. Subtotal parathyroidectomy should be considered only in the occasional patient who continues to show progression of the disease in spite of intensive medical therapy. Removal of three and three-fourths glands will usually be followed by prompt symptomatic improvement, resolution of ectopic calcifications, and healing of skeletal lesions.

The hypercalcemia that may occur following successful renal transplantation is usually transient and rarely justifies parathyroidectomy.

H. EARL GORDON, M.D.

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Goldman L, Gordon GS, Roof BS: The parathyroids—Progress problems and practice. *Curr Probl Surg*:1-64, Aug 1971

Zollinger-Ellison Syndrome (ZES)

DISTINGUISHING BETWEEN PATIENTS with severe duodenal ulcer disease and those with the Zollinger-Ellison Syndrome (ZES) is both difficult and vitally important. The classical description of marked gastric hypersecretion, severe duodenal or jejunal ulceration and diarrhea is seldom found until late in the course of the disease. Thus, patients with severe ulcer disease or the ZES may have similar symptoms, gastric secretory results, and roentgenographic findings. Hence, most patients have had previous operation for presumed duodenal ulcer disease before they were found to have a ZES. Tragically, this results in an increased mortality in this disease.

While serum gastrin determinations provide an objective test for the ZES, the procedure is time-consuming and not generally available. Recently it has been discovered that ZES patients produce large quantities of acid in response to infusions of calcium ions. This response is immediate and pronounced in that it equals or exceeds the maximal acid response in these patients. It is accompanied by a progressive rise in serum gastrin levels. Duodenal ulcer patients, in contrast, respond with a delayed and minimal output of acid. Calcium infusions are rapid, simple and safe. A calcium infusion, therefore, may be a useful diagnostic aid in patients with severe duodenal ulcer disease from ZES.

EDWARD PASSARO, JR., M.D.

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Passaro E, Basso N, Sanchez RE, et al: Newer studies in the Zollinger-Ellison Syndrome. *Amer J Surg* 120:138-143, Aug 1970

Management of Liver Injuries

INJURIES TO THE LIVER are almost twice as common today as a decade ago. Although they continue to result in high morbidity and mortality rates, particularly when they are associated with other organ injuries, there has been a dramatic increase in the salvage of patients sustaining either blunt or penetrating damage to the liver. This improved survival in recent years

is due primarily to an ever increasing awareness of the likelihood of liver injury in relation to the type of trauma, improvements in the general management of the severely traumatized patient, and appropriate and aggressive intraoperative techniques. The operation performed depends upon the extent of the liver injury and ranges from drainage alone to resective debridement combined with drainage and biliary decompression.

EARL F. WOLFMAN, JR., M.D.

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Lucas EE, Walt AJ: Critical decisions in liver trauma: Experience based on 604 cases. *Arch Surg* 101:277-283, Aug 1970

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New CMA Officers and Representatives



DR. CRUM

Dr. Jean F. Crum of Downey was installed as President of the California Medical Association at the annual meeting held February 12-16 in San Francisco, and Dr. Thomas N. Elmendorf of Willows was elected President-Elect by the House of Delegates.

Dr. Joseph F. Boyle, Los Angeles, was elected Speaker of the House, succeeding Dr. William F. Quinn, Los Angeles, who did not run for re-election. Dr. Quinn was voted into ex-officio membership of the House of Delegates in the newly-created position of Speaker Emeritus. Dr. Henry V. Eastman of Tustin was elected Vice-Speaker, succeeding Dr. Boyle.

Dr. Crum, who practices general and thoracic surgery, is a graduate of the University of Cincinnati's College of Medicine. He is a past president of the Los Angeles County Medical Association, an assistant clinical professor of surgery at the University of Southern California, a director of the American Cancer Society's California Division and an advisor to Regional Medical Programs' Area V.

Dr. Elmendorf, a general practitioner, is a graduate of Stanford University School of Medicine. He is an alternate delegate to the AMA, a member of the California Academy of General



DR. ELMENDORF

Practice, a past president of the Butte-Glenn Medical Society and is active in many Willows and Glenn County civic organizations.

Dr. Boyle, who earned his M.D. degree at Temple University, an internist, specializes in diseases of the chest. He is involved in scores of civic, medical and health organizations and is an associate clinical professor of medicine at the University of Southern California, a member of the State Air Resources Board, a delegate to the AMA, and chairman of CMA's Committee on Environmental Health.

Dr. Eastman, who is in general practice, lives in Santa Ana. He is a graduate of the University of Minnesota Medical School.

In other important elections, Doctors Simon C. Brumbaugh, Jr., Lemon Grove; Orrin S. Cook, Sacramento; William P. Frank, Alhambra; Carl Goetsch, Berkeley; Fred M. Kay, Fullerton; and Robert K. Salter, Stockton, were elected members of the CMA Council.

Doctors Walter H. Brignoli, St. Helena; Ralph W. Burnett, Bakersfield; and Crum were elected delegates to the American Medical Association. Doctors David S. Ardell, Bakersfield; Theodore F. Loring, Eureka; and Harold B. Miles, Santa Barbara, were elected alternate delegates.

A Power Base for Medicine

PUBLIC PRESSURES DIRECTED AGAINST medicine are increasingly apparent. They come from the executive, legislative and judicial branches of government and from the news media as well. Their power is enormous, at times even frightening. These trends are such that they raise a basic question as to whether or not the American public will be served better or worse in the long run if the influence of the medical profession in health care is substantially curtailed.

There is no escaping the fact that the medical profession is the life force of medical and health care. The quality and worth of this care is and always will be a reflection of the vigor and strength of the medical profession. It can be no other way. Therefore, quite clearly and simply, medicine has a duty and a responsibility to the American public to develop not only its competence and vigor, but to create a power base of sufficient strength so that it can play a far more, rather than a less, effective role in the complex arena of health care, an arena increasingly subsumed by others with less background and experience in health and its derangements, and also increasingly dominated by government.

Medicine has traditionally paid very little attention to what might be its power base in health care. This has been very little studied and there are many misconceptions. For example, some in medicine assume that the physician and his profession is or should be the unquestioned and final authority on everything to do with medical services and health care. While this may have been the case fifty or more years ago, it is certainly not today. Nor does the power base of medicine lie at the ballot box as others seem to think. One or two votes in a thousand count for very little, and at that physicians and even their

wives are unlikely all to vote the same way. Nor does medicine's power base rest with those whom it has helped to elect to public office. Realistically, anyone who is elected to public office will usually have been supported by many groups, most likely with different ideas, and often with greater numbers and substantially greater wealth. Not unpredictably, the record shows that public officials elected with the support of physicians often end up in opposition to the views of medicine. Nor does medicine's power base lie in any philosophy, whether this be "conservative," "liberal," or even the new "radical" philosophy espoused by some younger physicians. There is little of power in these approaches, and even less when differing philosophies lead to division, disagreement, discussion or paralyzing inaction within the profession. It seems clear that a truly effective power base for medicine must lie in something other than the traditional authority of the physician, his numbers, his much exaggerated wealth, or his hope that his particular philosophy of health care might be made to prevail. The fact is, these approaches have been tried and have simply not worked.

What then can be a power base strong enough to enable medicine to participate as a more effective and vital force in the arena of health care? Whence can come the necessary strength? There is much to suggest that public opinion has become the ultimate force which determines the course to be followed in this nation. The evidence for this is very considerable. It can be readily demonstrated that even the legislative, executive and judicial branches of government respond to this force. Therefore it is suggested that public opinion is the force which will decide the future of the medical profession and health care in this nation, and this is a force to be tapped and used for the advancement of medicine and the betterment of health care. If this is true, as it seems to be, then the question becomes how can medicine develop a power base which will utilize this force to give it the strength it must have to play a far more effective role in the arena of health care? This is the key question to be answered, and how it is answered

is likely to influence profoundly the future of medicine and health care for this nation for some time to come.

Several reports of the Committee on the Role of Medicine in Society have addressed themselves to a number of facets of this problem, and suggest that medicine must identify an ideologic base for its position in society, the scope of medical care with which it must deal, the essential functions of the physician, and then develop a technology for leadership and the exercise of social, economic and political pressures which will derive their power and strength from the understanding and support of public opinion. The studies suggest that within this kind of framework medicine can in fact develop a truly effective power base from which it can play a necessary and vital role for the advancement of the profession and the betterment of health care.

Very briefly, the aforementioned studies develop the thesis that an ideologic base may be found in medicine's concern with human biology and human disorders, in the biologic and therefore the sociologic uniqueness of every individual, and in the deep commitment of the medical profession to progress. The scope of medicine is found to cover a spectrum ranging from traditional care of the sick, injured and emotionally disturbed, through health care of persons not ill, health care delivery systems, community health, environmental and genetic or species health care. The essential functions of physicians were found to include (1) rendering a professional opinion with respect to health and its derangements, (2) participating in decision-making at all levels of health care, and (3) utilizing certain practice skills to perform a variety of procedures and services.

The technology for leadership will require equating the professional interest with the best interest of the public (which is not really very hard to do), demonstrating motivation, competence and a performance which is consistent with expressed policy statements by the profession and which merit the support of both membership and public opinion. *What to do* should be carefully decided on the basis of a clear identification of what the problem is, and the facts which bear upon the problem as these are measured against applicable value systems. *How to do it* should be through use of appropriate social, economic and political pressures in such a fashion that they

will always be clearly in the patient and public interest, and thus derive their strength from the support of public opinion. It should be noted in passing that the way these social, economic and political pressures are used in turn affects public opinion either favorably or adversely.

Again briefly, *social pressures*, that is pressures to inform and influence society, can be exercised best through communications, involvement and persuasion. Persuasion can be particularly effective if what is sought is considered to be reasonable, if the supporting arguments are valid and if there is public sympathy with the organization and its purposes. *Economic pressures* are now an accepted force in health care and are being used by health professionals, by health workers and by government. The time may soon arrive when medicine should develop more definitive techniques for the exercise of economic force or counterforce in the interest of patients, the public and better health care. The public must be in sympathetic support. It can be argued that it is in the patient and public interest that providers as well as consumers of health care be satisfied and that funding must be adequate if services are to be of high quality and in sufficient quantity so that all who need them may benefit. *Political pressures* can be of many kinds and their strength and effectiveness also depend very considerably upon the extent to which they are supported by public opinion. They may be direct, as upon an elected official whose campaign was supported, or indirect, as when exerted by others of like purpose. Negotiation becomes important when some compromise must be reached among forces of more or less comparable competence and strength. Again the terms sought should be reasonable, the supporting arguments valid, and the whole consistent with the interests of the profession and the public. Legislative and court action are further forms of political pressure, and these too must be in the public interest and interpretable as such, be reasonably consistent with the expressed policies of the association, be legally and politically possible, and have the support of public opinion, if they are to succeed.

It is suggested that medicine's true power base is much as has been described. The taproot of its strength lies in securing the understanding and support of public opinion. This power base already exists and it has enormous potential

strength. It has yet to be developed and used as effectively as it might. First it must be recognized for the force that it is by the profession and its leadership at all levels. The time is later than many might think.

—MSMW

Discontinuation of Routine Smallpox Vaccination

NOW THAT THE UNITED STATES has been free of smallpox for 28 years, serious concern has been felt about the morbidity and mortality which has resulted from vaccination itself. In recent years there has been an average of seven deaths annually and numerous severe sequelae. A great many of these complications are avoidable, but they have raised the question of whether universal or routine vaccination is worth this risk.

This comes at a time when mass efforts for immunization, spurred by the World Health Organization, have resulted in near elimination of the disease in areas where constantly recurring epidemics have prevailed. According to the morbidity and mortality report for January 22, 1972, from the Center for Disease Control, U.S. Public Health Services (HEW), smallpox occurred in 42 countries in 1967, in 23 countries in 1970 and in 17 in 1971. During the last six months smallpox was reported from only four countries—India, Pakistan, Ethiopia and Sudan. Mexico has been free of variola since 1955 and Brazil has escaped for the past two years.

After several years of spirited debate the recommendations of the U.S. Public Health Service, the California State Department of Health, and the Committee on Infectious Diseases of the Academy of Pediatrics now state that vaccination in infancy or before school attendance should be abandoned as a routine and should be restricted only to those for whom there is significant risk of exposure—that is, those in the Armed Services, others who plan to travel in endemic areas, and physicians, nurses, hospital attendants and other health personnel in the United States who are at the greatest risk of exposure to the possi-

ble imported case. In England and Europe, half the cases contracted from exposure to those of foreign origin occurred in hospital personnel.

Primary vaccination could be expected to occur in adults who have not been previously vaccinated. It is now believed that primary vaccination of adults will not result in increased frequency of sequelae; formerly, it was accepted that the contrary was the case. The unexplained horrendous incidence of complications in military recruits in the Netherlands may be recalled.

Modern transportation has increased the threat of importing cases. It is necessary only for an unimmunized person to have been intimately exposed 14 days before arrival in the United States to be responsible for infection of contacts. So far, this has not been a problem. However, in Britain, 13 imported cases occurred between 1951 and 1970, followed by 103 secondary cases and 37 deaths. During this same period, however, there were 100 deaths from smallpox vaccination. (The figures for this statement were supplied by Dr. C. Henry Kempe, probably the best authority on smallpox in the United States.) Prompt recognition of the imported disease would make it possible to vaccinate all contacts; the use of the drug methisazone (Marboran®) may make it possible to control spread even further.

This disease is stated to be less infectious than influenza and measles, although this is contrary to what most of us previously believed. It must be borne in mind that the smallpox scab can transmit the disease after two years if kept dry and at room temperature, unlike the scab of vaccinia or chickenpox, which loses virulence quickly.

In spite of so-called compulsory vaccination, the prevailing level of immunity in the United States is so low that vaccination cannot be credited with the eradication of smallpox. It must be remembered, however, that practically every important pathogen has had an inexplicable wax and wane in occurrence and severity: staphylococci, meningococci, *B. pestis*, *C. diphtheriae*, influenzae virus, etc. The present weight of evidence seems to support the discontinuation of vaccination as a routine procedure. However, no matter how reasonable and acceptable this may appear (*which it does*) it poses a number of problems which must be faced by the physician:

1. Smallpox vaccination has been an almost

ered institution in the public mind and credited with the "conquest" of variola in the United States. However, public reeducation, "dis-education," is a hazardous matter. The "anti's" of all persuasions will be filled with glee and will assert that vaccination has not been responsible for the decrease of this disease in this country at all. In these days, when oversimplification characterizes the news media dissemination of scientific information, this may lead to distrust regarding other forms of immunization which have also been authoritatively proposed as a necessity. It may lead to such questions as is there a communication gap or, worse, a conflict of interest? This might prove to be a threat to other immunizations which are so well established and beneficial.

2. We grant that routine vaccination should be continued for all health and hospital personnel. At this moment, a crash program for these persons is proposed; but it should not be forgotten that pediatric wards will be filled with unvaccinated children who will be at significant risk of contact with those with primary vaccination takes. Children under treatment with steroids or those with eczema or malignant disease, or with immune deficiencies (which group make up a large proportion of children in today's pediatric ward) will be at risk of exposure to these attendants. Eczema vaccinatum, often fatal, usually results from exposure of an eczematous child to a recently vaccinated contact. Health personnel probably should be vaccinated during vacations and not permitted to expose today's hospital patients who are especially vulnerable, including some adults and many children. This precaution has been largely ignored in the past.

3. Routine vaccination must be continued for those in the Armed Forces. A great many of the present recruits have been vaccinated in early childhood; for them, revaccination is a relatively benign procedure. In the future, primary vaccination in recruits will constitute a new hazard of severe reactions and late sequelae at a time when they are subjected to a number of other immunizations.

It has been proposed that attenuated or killed vaccine may be employed for these as a preliminary measure, but this product is not yet available, and will be hard to come by.

4. If a patient has imported smallpox, who will be responsible for the diagnosis? Most of

today's physicians have not seen a single case; it is possible that suspicion of the diagnosis might be long deferred and permit the number of contacts to become extensive. A few years ago near-panic was set off by a misdiagnosed patient who was finally discovered to have chickenpox. More than 25 years ago, in the last imported case (in San Francisco from Asia) the patient died, shortly after arrival, with the diagnosis of purpura hemorrhagica. The final diagnosis was established only after several deaths among several doctors, nurses, the undertaker and other contacts in whom smallpox had developed.

5. Some physicians have asked whether a child who has now been vaccinated at the age of one year should be revaccinated on reaching school age in order to have his immunity prolonged. This is probably not a matter of great importance with this new recommendation for, once having a primary take, the child will have limited vulnerability to exposure and almost no risk of fatal smallpox.

The abandonment of smallpox vaccination will thus not put an end to all existing questions about this disease and immunization for it. Previously, vaccination was compulsory by legislation. The present statements from various authorities are simply recommendations to abandon compulsory vaccination. It will permit the physician to follow his personal judgment in a variety of situations but may make his defense difficult if unpleasant sequelae follow vaccination without any special indications.

EDWARD B. SHAW, M.D.

*Department of Pediatrics
University of California, San Francisco*

Multidisciplinary Teamwork In the Management of Childhood Cancer

THE ARTICLE IN THIS ISSUE by Finklestein and Gilchrist, "Recent Advances in Neuroblastoma," illustrates repeatedly the importance of new dimensions of multidisciplinary teamwork in the management of cancer.

Neuroblastoma is an important cancer of children, the therapy for which leaves much to be learned. It is a unique tumor in several respects. It is most common in early infancy; it has an impressive history of spontaneous regression, and its natural history is highly predictable when age of the patient, histopathologic classification and accurate clinical staging are considered.

It apparently has specific cellular antigenic components, and, like some trophoblastic tumors, it secretes characteristic metabolic products which can provide "markers" permitting detection of residual tumor following operation, occult metastasis, or early recurrence.

Finklestein and Gilchrist stress the importance of a complete patient evaluation before therapy, from which a multidisciplinary treatment plan can be developed. They propose "second look" surgical operation after a significant tumor-free interval, and they raise the intriguing possibility of immunotherapy for this tumor. They also wisely point out the special insights and experience required of radiation therapists who treat infants and children.

Their review places in perspective a cancer which demands the concerted skills of pathologist, bio-chemist, immunologist, radiologist, surgeon, radiation therapist, pediatric oncologist and family physician. The review presents lessons for all of these disciplines and for geneticists and embryologists as well.

During the past decade, substantial progress in treatment of childhood cancer has been made. The most favorable treatment programs for acute leukemia are expected to produce median survival of over four years, and apparent "cures" are being referred to with increasing confidence. Similarly, with childhood solid tumors the co-ordination of more aggressive, multidisciplinary therapeutic plans is leading to prolonged tumor-free survival and improved cure rates.

These encouraging results are not being obtained solely because of new therapeutic discoveries, nor are they being obtained by all who treat children with cancer. They are being seen at institutions where basic and clinical investigators have developed sophistication in combining their best skills and have systematically applied many pieces of useful information that have been gathered painstakingly from careful investigation.

Thus, while several years ago it mattered little

where or by whom a child with cancer was treated, it has begun to matter a great deal. A child with a tumor now deserves evaluation by a team representing all of the disciplines that may have a role in developing the best therapeutic plan.

An appropriate evaluation of a child with a tumor and the development of an individualized plan of therapy will involve accurate histopathologic classification, clinical staging of extent of involvement, and often bio-chemical, immunologic, and isotopic examinations. The contributions to therapy and the appropriate timing of surgical operation, radiation therapy, chemotherapy and, soon, immunotherapy, must all be weighed in developing an optimal therapeutic plan. Moreover, the requirements for teamwork and co-ordination continue as the plan is carried out and new problems arise which also require varied skills.

Institutions expecting to provide good care for children with tumors should have such teams. Institutions that do not establish such teams should refer patients with cancer to those that do. Such teams are necessary to provide the multidisciplinary interaction that can now produce good outcome for some cancers. Patients with tumors which are refractory to current treatments, also should be referred to such institutions, since the accumulation of experience through co-ordinated multidisciplinary investigation provides the greatest opportunity for substantial improvement of current treatments that are still not good enough.

DENMAN HAMMOND, M.D.

*Associate Dean
USC School of Medicine
Director
University of Southern California
Cancer Center
Los Angeles*

Lymphocyte Tissue Culture In Transplant Surgery

TO USE LYMPHOCYTE or leukocyte tissue culture in the monitoring of human transplants is to apply a laboratory technique with many potential pitfalls in both interpretation and quantitation¹ to a complex clinical situation. Nevertheless, us-

ing this technique, it is often possible to gauge *in vitro* the prevailing immunological trends in a given transplant patient. Unfortunately, in a possible rejection period where time is at a premium, with the method currently in use it takes days to get an answer.

Looking at the overall picture, one is encouraged by the report of Bach et al.,² in which a good correlation was noted between the results of mixed lymphocyte cultures in 36 patients before operation, and function of their renal transplants after one or two years. None of the patients with a creatinine clearance over 70 ml per minute had originally had more than 5 percent transformed cells in their cultures. Kidney allograft survival in mongrel dogs has been similarly studied by Kiskin and Malek.³

Lymphocytes taken from a patient satisfactorily suppressed have been variously and contradictorily reported to respond normally *in vitro* or to have diminished responsiveness. Heine et al.⁴ found that the depression of response to phytohemagglutinin was only insignificantly lower in a group of 30 patients being treated with 6-mercaptopurine or azathioprine when compared with a group of 54 normal controls. Joseph similarly found no change in lymphocyte response to phytohemagglutinin during rejection episodes.⁵ However, most other workers have found that patients with a satisfactory level of immunosuppression have a reduced phytohemagglutinin response and that a return to normal responsiveness *in vitro* heralded a rejection crisis or a deterioration in renal function.^{6,7,8}

Preceding rejection episodes there also appears to be an increased traffic in the blood of activated lymphocytes similar to that associated with vaccination or virus infection. This is readily detected either by counting atypical mononuclear cells in the peripheral blood, or by measuring the increased rate of RNA synthesis in peripheral blood mononuclears in a two-hour culture.⁹ Both of these approaches have the merit of giving prompt answers. The presence of activated cells in the circulation is also reflected in an increased rate of spontaneous transformation in leukocyte cultures.^{8,10,11}

Having detected increased immunological activity in a transplant patient, one is faced with the question, is this a desirable response to a pathogenic microorganism or a prelude to rejection? One is hard put to know unless some im-

munological specificity is introduced into the culture system such that an increased responsiveness of the patient's lymphocytes to the antigens of the allograft can be measured. This object would probably best be achieved by using serial mixed cultures along the lines of those reported by Oppenheim et al.,¹² who clearly demonstrated a temporarily enhanced response coincident with episodes of skin graft rejection. Liquid nitrogen banking of viable lymphocytes taken from the donor at the same time as the allograft presents no major technical problems.¹³

Apart from changes in the lymphocyte population in the blood before rejection episodes, there is also a change in the serum level of α_2 globulin, a lymphocyte inhibiting protein. The latter has been reported to be elevated to the point where serum taken from renal transplant patients during rejection episodes causes a decrease in thymidine uptake by lymphocyte cultures.¹⁴ The variable content of patient's serum in cultures of his lymphocytes along with technical variation in the preparation of his cells might explain some of the contradictory reports on responsiveness to phytohemagglutinin.

Lymphocyte tissue culture has wide application in clinical studies,^{15,16} and one of its more useful applications may be in the monitoring of transplant patients.

ALAN S. COULSON, PH.D.

Stanford University School of Medicine

ROY COHN, M.D.

Professor of Surgery

Department of Surgery

Stanford University School of Medicine

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Water Intoxication in a Beer Drinker

BEER PRODUCES A NUMBER of well known physiologic effects, including a water diuresis which is due to an inhibition of anti-diuretic hormone (ADH) release by both the alcohol¹ and the water contained in beer, and a central nervous system intoxication which is ordinarily due only to the alcohol. Elsewhere in this issue of CALIFORNIA MEDICINE, Gwinup et al report the (fortunately) uncommon association of beer ingestion and water intoxication.

A 46-year-old man with a history of having drunk 3 to 6 liters of beer daily for many years presented to the hospital with mental confusion on three separate occasions over a three-year period, and on each occasion he was found to have significant hyponatremia. Serum osmolality was low, demonstrating dilution of total extracellular solutes by water, and urine osmolality was quite high, indicating inappropriate ADH release; however, preliminary study failed to reveal any of the recognized causes of inappropriate ADH release.² If it is assumed that the patient ordinarily tolerated his large daily beer intake without suffering water intoxication, the most likely diagnosis is intermittent or temporary inappropriate ADH release of uncertain cause.

An attempt was made, in the present case, to assess the role played by the ingestion of 5 liters of beer a day, by comparing the effects of one week of beer ingestion, one week of an equivalent amount of water ingestion, and one week of concentrated alcohol ingestion (about 220 grams a day, the amount present in 5 liters of 4.6 vol% beer). Beer ingestion was accompanied by a rising urine osmolality as well as

progressive weight gain and hyponatremia which abated abruptly when beer was discontinued. Water ingestion was accompanied by a very slowly falling urine osmolality, as well as some water retention and hyponatremia which abated as the urine gradually became very slightly hypotonic during the last few days of water ingestion. Alcohol ingestion apparently failed to produce either a hypotonic urine or a detectable change in water balance. The authors concluded that beer, per se, may have produced the inappropriately concentrated urine, but allowed for the possibility that the different effects observed between beer ingestion and water ingestion may not have been related to any such effects of beer independently of its water content. What makes the latter possibility attractive is that an abnormality of ADH release, not dependent on beer intake, is strongly suggested by the apparent failure of water or alcohol to result in the production of maximally dilute urine. Furthermore, as was mentioned, the patient may well have tolerated large beer loads on many occasions outside the hospital without developing water intoxication. For these reasons, it seems not unlikely that a non-osmotic factor other than beer—for example, acute anxiety, unusual excitement, abrupt increase in tobacco use, and certain drugs²—is causing intermittent and variable release of ADH which resulted in the patterns observed during the periods of study, and which, out of hospital, resulted in water intoxication whenever sufficiently large amounts of water, in the form of beer, also happened to have been ingested. If this interpretation is correct, the role played by beer in the present case is well summarized by the motto appearing on the label of the test beer employed by the authors—"It's the Water."

Finally, although the association of excessive beer intake and water intoxication is certainly an oddity, the present case should serve as a reminder of an entity which, in all likelihood, is not an oddity—that is, temporary inappropriate ADH release, excessive "free-water" intake, and water intoxication.

TERRANCE M. DAUGHARTY, M.D.

Assistant Professor of Medicine
University of California, San Francisco
Department of Nephrology
Veterans Hospital, San Francisco

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CASE REPORTS

Refer to: Gwinup G, Chelvam R, Jabola R, et al: Beer drinker's hyponatremia — Inappropriate concentration of the urine during ingestion of beer. *Calif Med* 116:78-81, Mar. 1972

Beer Drinker's Hyponatremia

Inappropriate Concentration of the
Urine During Ingestion of Beer

GRANT GWINUP, M.D., *Orange*;
REG CHELVAM, M.D., REUBEN JABOLA, M.D.,
AND LESTER MEISTER, M.D., *Long Beach*

IN THE PAST SEVERAL YEARS we have seen a number of beer drinkers who have been admitted with striking hyponatremia, although we have been unable to find any reference to this condition in the literature. We report studies performed on such a patient in an attempt to establish the association between beer ingestion and hyponatremia and to gain information regarding the mechanism of the production of hyponatremia.

Report of a Case

The patient was a 46-year-old Caucasian man who was admitted to the Long Beach Veterans Administration Hospital 11 May 1970 with complaint of weakness and mild confusion. He gave a history of many years of drinking between six and twelve 16-ounce cans of beer a day. Consumption tended to be greater during the warmer summer months. For the preceding two weeks he had averaged eight to ten cans of beer daily.

From University of California, Irvine, California College of Medicine, and Veterans Administration Hospital, Long Beach.

Submitted April 19, 1971.

Reprint requests to: G. Gwinup, M.D., Department of Endocrinology and Metabolism, Orange County Medical Center, 101 S. Manchester Avenue, Orange, Ca. 92668.

He denied vomiting or diarrhea and insisted that he maintained a reasonably normal dietary intake.

On examination of his hospital record it was found that he was admitted with similar but more severe complaints 15 July 1968, at which time his serum sodium content was 106 mEq per liter and again 8 June 1969, when serum sodium was 111 mEq per liter. On each of these occasions he was decidedly confused, but each time confusion abated spontaneously during the first several days in hospital without specific treatment. Past history revealed that for many years he had complained of selective weakness of the lower extremities, which had been ascribed to a peripheral neuropathy.

On physical examination he appeared well-nourished. The blood pressure was 150/90 mm of mercury and the pulse 78 per minute and regular. The neck veins were not distended and the thyroid gland was not enlarged. The chest was clear to auscultation and percussion, the heart of normal size and without abnormal sounds. The abdomen was soft, and there was no evidence of ascites. The liver was not enlarged. There was no pretibial edema. Muscular strength was essentially normal over most of the body but was symmetrically reduced in the lower extremities. Reflexes, sensation to pinprick, and proprioception were also diminished in the lower extremities.

On admission the hemoglobin was 14.1 grams per 100 ml, hematocrit 42 percent, white blood cell count 5,600 per cu mm with 62 percent polymorphonuclear cells and 38 percent lymphocytes. Specific gravity of the urine was 1.018 and it contained no protein, glucose, acetone or cells. Serum sodium was 122, chloride 84, potassium 5.1, and bicarbonate 24 mEq per liter, blood urea nitrogen 8 mg, cholesterol 232 mg, total protein 7.8 grams (albumin 3.3 grams) and fasting glucose 85 mg per 100 ml. scot was 33, alkaline phosphatase 9.5 King-Armstrong units, total bilirubin 0.8 mg per 100 ml, creatinine clearance 82

ml per minute, *Bromsulphalein*® retention 4 percent at 45 minutes, prothrombin time 70 percent, protein-bound iodine 4.4 µg per 100 ml, and urinary 17 ketogenic steroids 8.9 and 17 ketosteroids 19.7 mg per 24 hours. X-ray films of the chest and the skull and an intravenous pyelogram were within normal limits. A brain scan was normal. Urinary porphyrins were normal.

No specific treatment or supplemental sodium was given, but within three days the patient's serum sodium had returned to 142 mEq per liter, his confusion had abated, and his strength was greatly improved.

Materials and Methods

Studies were conducted over a 35-day period while the patient was maintained on a general diet with no fluid or salt restriction. After a short baseline period, ten 16-ounce cans of beer containing alcohol 4.6 percent by volume and sodium 16 mg per liter were given over 16 hours of every day for seven days. This was followed by a control period of one week, after which ten 16-ounce beakers of water were taken over the same period of every day. After another control period, a quantity of alcohol equal to that contained in the beer was administered as 50 percent ethyl alcohol in seven doses of 2 ounces every two hours. Serum was obtained daily for determination of sodium, chloride, potassium, bicarbonate, and blood urea nitrogen. The volume and osmolality of each day's urine was measured, and the patient's weight and fluid intake were recorded daily.

Results

BUN ranged from 7 to 12 mg per 100 ml and showed no significant change throughout the study. During the period in which beer was administered, urinary sodium ranged between 33 and 47 mEq per 24 hours (mean = 42 mEq per 24 hours) with no significant change. At the beginning of the period of beer ingestion, the hemoglobin was 16.3 grams per 100 ml and the hematocrit was 47 percent. Ten days later, when the serum sodium had fallen to its lowest value, the hemoglobin was 14.3 grams and the hematocrit was 42 percent. At the end of the study the hemoglobin was 15.8 grams and the hematocrit 48 percent. At no time was the serum lipemic. The changes which occurred in serum electro-

lytes, body weight, and urinary osmolality are plotted in Chart 1 and the 24-hour total fluid intake and output volumes are recorded in Table 1.

During the period in which beer was administered, there was a progressive decrease in serum sodium, which had reached 123 mEq per liter on the last day of beer ingestion. Hyponatremia was accompanied by a comparable hypochloremia with minimal changes in serum potassium concentration. Changes in serum osmolality closely paralleled changes in serum sodium falling progressively from an initial value of 293 to 253 milliosmol per kilogram on the last day of beer ingestion. Body weight rose 8 pounds during the same period, and fluid balance was strongly positive, averaging almost 1,300 ml daily. Beer ingestion was accompanied by an inappropriately concentrated urine which remained above 800 milliosmol per kilogram throughout the last three days of the period.

Water ingestion produced an early decrease in both serum sodium and chloride concentration, but both returned to normal as the period continued. Body weight fell off slightly, and the urine became dilute averaging less than 300 mOs per kilogram. After the first two days, positive fluid balance was of far less magnitude than it was during the period of beer ingestion.

The ingestion of alcohol alone produced little or no change in serum electrolytes, body weight or fluid balance.

Discussion

In this patient the ingestion of large quantities of beer resulted in the production of concentrated urine, a pronounced increase in body weight, strongly positive fluid balance, and a rather striking degree of hypotonic hyponatremia which was presumably largely or wholly dilutional.

The combination of hypotonic serum and concentrated urine is often regarded as presumptive evidence for the inappropriate production of antidiuretic hormone. Although this state may occur as a consequence of bronchiogenic carcinoma and a number of other diseases, it has also been described in otherwise healthy persons, in whom it may be a self-limited condition.¹

It is possible that in our patient ingestion of large quantities of beer served to unmask a tem-

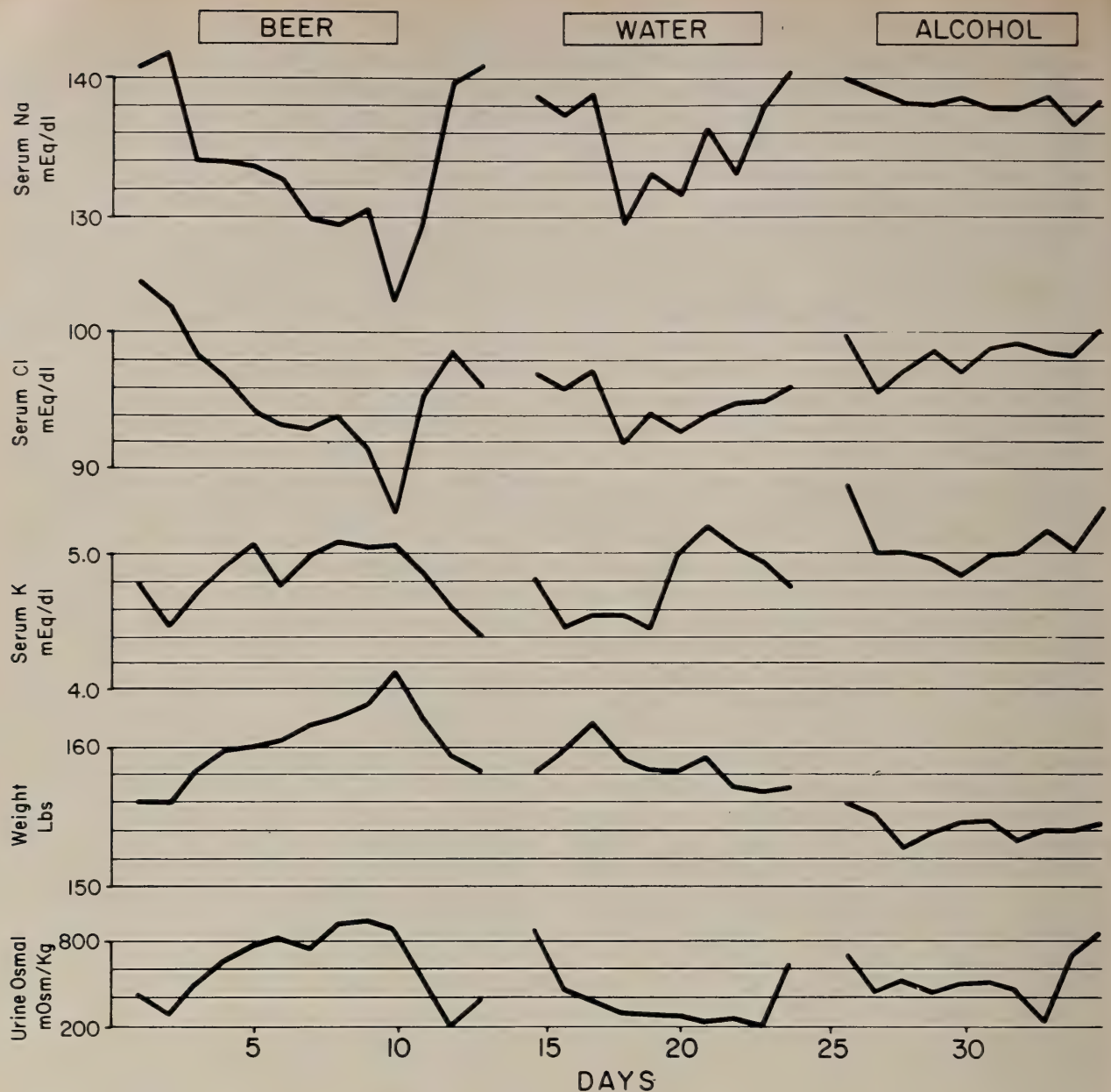


Chart 1.—Changes in serum electrolytes, body weight and urinary osmolality during periods of ingesting beer, water and alcohol

porary inability to dilute urine unrelated to any constituent of the beer except its water content. This explanation is supported by the unsustained decrease in serum sodium concentration in the first few days of the period of water ingestion. The hyponatremia of beer drinking might therefore be similar to the hyponatremia of the compulsive water drinker described by Hobson and English, in whom inappropriate antidiuretic hormone secretion was thought to play a permissive role.²

It is also possible that beer produced hypona-

tremia and inappropriate concentration of the urine by an unknown mechanism completely apart from inappropriate antidiuretic hormone secretion.

In our studies a fourth period was initiated in which 14 ounces of 50 percent ethyl alcohol and 160 ounces of water were administered daily, but the patient did not cooperate and this effort had to be abandoned. Additional studies will be necessary to determine the frequency of this syndrome and to further elucidate the mechanism by which it is produced.

TABLE 1.—Daily Fluid Intake, Output and Balance Induced by Ingestion, Each for a Seven-Day Period, of Beer, Water and Alcohol

	PERIOD		
	Intake (ml)	Output (ml)	Balance (ml)
BEER	5,810	4,120	+1,690
	5,400	4,160	+1,240
	5,930	5,100	+830
	5,800	4,680	+1,220
	5,690	4,220	+1,470
	5,480	4,410	+1,070
	5,910	4,100	+1,810
WATER	5,950	4,460	+1,490
	5,950	4,640	+1,310
	6,140	6,100	-20
	5,410	5,110	+300
	5,970	5,460	+510
	6,160	5,820	+340
	5,880	5,310	+490
ALCOHOL	2,100	1,910	+190
	1,960	1,440	+529
	1,680	1,210	+470
	1,400	1,640	-240
	2,010	1,770	+840
	1,640	1,240	+400
	1,500	1,180	+380

Summary

Studies were performed on a patient who had repeatedly presented to the hospital with profound hyponatremia following the consumption of large quantities of beer. The administration of 160 ounces of beer per day produced hyponatremia, weight gain, strongly positive fluid balance and inappropriate urinary concentration. It is concluded that in this patient the ingestion of large quantities of beer either unmasked or produced the syndrome of inappropriate concentration of the urine.

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ADDENDUM: In the time between the preparation and the publication of this report Demanet et al* reported a similar group of patients with the same syndrome. All were heavy beer drinkers and presented with coma and striking hyponatremia.

JAMA printed an editorial on the subject in February of this year.†

*Demanet JC, Bonnyns M, Bleiberg H, et al: Coma due to water intoxication in beer drinkers. *Lancet* 2:1115-1117, 1971.

†Water-intoxicated beer drinkers (Editorial). *JAMA* 219:1060, Feb 21, 1972.

Refer to: Lewis JE, Sampson WI: PTC deficiency with phalangeal and interphalangeal (arthritic) changes. *Calif Med* 116:81-85, Mar 1972.

PTC Deficiency with Phalangeal and Interphalangeal (Arthritic) Changes

JAMES E. LEWIS, M.D., AND
WALLACE I. SAMPSON, M.D., *San Jose*

FACTOR IX (plasma thromboplastin component, Christmas factor) deficiency or hemophilia B, like its counterpart factor VIII (antihemophilic globulin) deficiency or hemophilia A, is a well known cause of frequent and disabling episodes of bleeding into the larger joints of the body.^{1,2,3} Bleeding occurs in approximately the following order of frequency: knees, elbows, ankles, shoulders, hips and wrists. Except for major bleeding episodes associated with specific traumatic events,^{4,5,6} reports describing the changes that occur in the phalangeal and interphalangeal joints are rare.^{1,2,4,7}

This communication presents the clinical history, physical examination, laboratory data, x-ray films and photographs of the changes which have occurred in the interphalangeal joints of a 29-year-old Caucasian man with severe PTC deficiency.

Report of a Case

The patient, a 29-year-old Caucasian man, had had bleeding at the site of circumcision shortly after birth. This led at that time to investigation at Stanford-Lane Hospital, San Francisco, where the diagnosis of severe plasma thromboplastin component (PTC) deficiency was established. Throughout early childhood he had numerous

From the Department of Medicine, Santa Clara Valley Medical Center, San Jose and Department of Medicine, Sunnyvale Medical Clinic, Sunnyvale.

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Reprint requests to: J. E. Lewis, M.D., Department of Medicine, Santa Clara Valley Medical Center, 751 South Bascom Avenue, San Jose, Ca. 95128.

episodes of acute major bleeding as well as minor bleeding into the knees, ankles, elbows and wrists with relative sparing of the proximal joints. Bleeding was noted on one occasion from the urinary tract and on several occasions in moderate amounts from the gastrointestinal tract. Casts had been applied to his lower extremities on various occasions. Prophylactic transfusions of blood and later plasma were given throughout many of his childhood years, usually at two-week intervals.

At age six he was confined to a wheelchair because of progressing contractures of both knees. He was treated for one year with casts and wedging to both extremities. This partially corrected his knee contractures and he resumed walking with aid. The contractures recurred following removal of the casts. Gradually, as a result of frequent large and small bleeding episodes almost complete ankylosis of the elbows developed, and the range of motion of both wrists became extremely limited.

From 1952 until 1967 he received prophylactically one unit of plasma a week. During this time he did quite well, having only a few minor bleeding episodes. However, when prophylactic transfusion was stopped for 18 months, he had prolonged episodes of pain and decreased mobility of the shoulders, elbows and hips, and several instances of acute bleeding. (These episodes were treated with plasma.) Weekly prophylactic transfusions of plasma were resumed in mid-1968, with functional improvement and a decrease in frequency of major bleeding episodes. The patient never had had major bleeding episodes involving the fingers.

In early 1969 he began receiving 500 units of factor IX concentrate (Konyne®)* every two weeks prophylactically and has had only minor episodes of bleeding into the knees and toes in the past twenty months. The frequency of replacement of factor IX concentrate was increased to 500 units weekly while the patient underwent more active physical therapy and rehabilitation.

In July 1970 the physical examination was entirely normal with the exception of the musculoskeletal changes. Mild limitation of cervical motion was noted, along with bilateral shoulder ankylosis. The right elbow was ankylosed and the left elbow showed only minimal motion. The right wrist showed slight ulnar deviation and



Figure 1.—Left hand. Fusiform enlargement of PIP joints and thickening of the DIP joints.

moderate limitation of motion. The knees were fixed in approximately 45 degrees of flexion and ankle motion was moderately restricted on the left and mildly restricted on the right. There was mild enlargement and decreased range of motion of all the metatarsal-phalangeal joints and interphalangeal joints of the toes. Range of motion of all the fingers was decidedly limited, with approximately thirty degrees flexion contracture of the proximal interphalangeal joints (PIP) and lesser degrees of contracture of the distal interphalangeal joints (DIP) bilaterally. There were mild enlargements and thickening of the distal interphalangeal joints of both hands, with the left second DIP joint and the right third DIP joint and thumb being moderately enlarged. All of the PIP joints showed moderate fusiform enlargement, especially the left second finger (Figure 1). There was minimal rotation of the metacarpophalangeal joints of both thumbs and pronounced limitation of abduction of the left thumb. There were no subcutaneous nodules.

The patient could propel his own wheel chair, transfer from chair to bed, and drive his car without assistance. He was able to hobble for very short distances in a stooped position and could hold a pen and write legibly with his left hand.

*Konyne® (human factor II, VII, IX, X complex) Cutter Laboratories, Inc., Berkeley.

The family history is essentially negative for hematologic and arthritic problems with the exception of non-specific lumbosacral "arthritis" in both parents occurring after the fourth decade.

Laboratory evaluation in 1966 revealed a partial thromboplastin time (PTT) of 102 seconds (normal range 33-44 seconds). Quantitative PTC assay was less than 1 percent.* In 1969 the PTT was 81 seconds, factor IX assay was 1.4 percent and no factor IX inhibitor was demonstrated.† Testing for genetic variants of factor IX was not done. Rheumatoid factor hemagglutination test was positive at 1:400 in August 1966 and again in December 1970.‡ Sedimentation rate was 20 mm in one hour in December 1970 during quiescence of symptoms. In June 1971 a lupus erythematosus cell test, VDRL test, anti DNA (less than 10 units; normal less than 20) and antinuclear antibody (immunofluorescent antibody, negative at 1:10) were all normal. Protein electrophoresis was normal with the exception of a very mild, diffuse gammaglobulin elevation of 1.59 mg per 100 ml (normal 0.5 to 1.5 mg).

Radiographic changes in the hands in 1962 (Figure 2) were minimal compared with those of September 1970 (Figure 3). The latter revealed slight bony demineralization and no evidence of ulnar deviation of the phalanges at the metacarpal phalangeal joints. The carpal bones were fused and there was pronounced alteration and almost complete obliteration of the radiocarpal and carpal-metacarpal joints. Multiple cystic changes were seen in the carpal bones as well as the second and third distal metacarpals on the right and the second metacarpal on the left. Narrowing of several metacarpal joints was seen. Narrowing of the PIP joints with cystic changes and eburnation was noted along with some subluxation and flexion deformity. The DIP joints appeared to be spared and the soft tissues were unremarkable.

Discussion

Before the recognition of factor IX deficiency by Aggeler and coworkers in 1952, the distinction between factor VIII and factor IX deficiency was not apparent in case reports and discussions on hemophilia.⁸ In 1936, Thomas reported involvement of the fingers in 15 of 98 patients with



Figure 2.—Hands, 1962. Carpal-metacarpal fusion but minimal interphalangeal changes.



Figure 3.—Hands, 1970. Narrowing of proximal interphalangeal joints with cystic changes, eburnation, subluxation and flexion deformities.

hemophilia but noted permanent changes in only two.³ Most large series since then would indicate that bleeding into the interphalangeal joints of the fingers is considerably less common.^{1,2,9,10,11,12,13} Webb in 1960 reported 39 cases of hemophilia A and three of hemophilia B. Nine of the patients had finger involvement but it is not apparent whether any of the patients with hemophilia B had finger involvement.⁷ He noted that osteoporosis of the hands was commonly present without symptoms or signs of local joint involvement.

Passing mention of involvement of the fingers in hemophilia B is sparsely scattered throughout the literature but with minimal detail as to severity or relative frequency.^{6,12,13,14} To our knowledge the only patient with factor IX deficiency with finger involvement reported in the literature was that described by Ahlberg.¹ He

*Performed by Dr. Judith Pool, Stanford University School of Medicine

†Performed by Dr. Carol Kasper, Los Angeles Orthopedic Hospital

‡Performed by Dr. Wallace Epstein, University of California, School of Medicine, San Francisco

reported that of 157 hemophiliac patients studied, four had lesions of the small joints of the hands and fingers and all four had severe disease (factor VIII or IX assay less than 1 percent). The only one of these that had PTC deficiency had "grade 3" involvement of both hands, but specific bone and joint changes were not described except for "contracture of the fingers."

In hemophilia, pseudotumor of the phalanx may result from a single traumatic event and proceed to periarticular swelling as well as cystic and destructive changes radiographically.^{4,5} Prior⁴ concluded that this represented the end result of bleeding into a small articulation but that progressive destruction and cutaneous rupture may result instead of the regression and ankylosis which occur in the large bones and joints. Jordan illustrated the radiographic changes of the fingers and hands of a 15-year-old patient with hemophilia (type unspecified) with involvement of "every articulation of the upper and lower extremity" including all the fingers.² Moseley depicted the changes in a patient with advanced hemophiliac (type unspecified) arthropathy showing obliteration of the radiocarpal joint.¹⁵ The opposing articular surfaces were eroded and there were numerous subchondral cysts at the distal end of the radius and in the navicular and lunate bones. Cortical eburnation and subcortical sclerosis was also evident.

Although the changes in the joints in the present case cannot be differentiated easily from those of rheumatoid arthritis, the absence of acute inflammatory episodes and subcutaneous nodules, the greater involvement of the distal interphalangeal joints and the fact that morning stiffness was minimal argue against the diagnosis of rheumatoid arthritis as the sole cause. The lack of more extensive bony demineralization and the rheumatoid factor hemagglutination titer of 1:400 (positive in second tube dilution) in the nonspecific range* substantiate this thesis. The negative anti DNA, antinuclear antibody, VDRL and LE cell test are evidence against other autoimmune processes (for example, systemic lupus erythematosus).

It should be noted, however, that pathologic joint changes following intraarticular injection of heterologous fibrin in animals have been found to resemble those of rheumatoid arthritis microscopically as well as in their chronicity.¹⁶ The

present case, with the unusual tissue reaction to minor bleeding episodes and perhaps increased propensity to rheumatoid arthritis, may represent a point in the spectrum of hemophilia and rheumatoid arthritis. Further studies on the roll of fibrin deposition in man and its relation to hemophilia and rheumatoid arthritis may increase our understanding of this process.

Summary

An unusual case of severe factor IX (plasma thromboplastin component) deficiency in a 29-year-old man demonstrating phalangeal and interphalangeal joint involvement is presented. Demineralization, cystic changes and proximal interphalangeal joint narrowing were seen radiographically and synovial thickening of these joints was palpable clinically. The rheumatoid factor hemagglutination test was positive, but in the nonspecific range. This report is the first detailed description of phalangeal and interphalangeal changes in PTC deficiency which appear to have resulted from repeated minor intra-articular bleeding episodes rather than major traumatic incidents. The rheumatoid changes, distinctly unusual in PTC deficiency, might simply be changes that in other circumstances would have been "subclinical" rheumatoid arthritis, and may represent a point in the spectrum of the arthropathy of rheumatoid arthritis and hemophilia.

TRADE AND GENERIC NAMES OF DRUGS

Konyne®.....factor IX complex (human)
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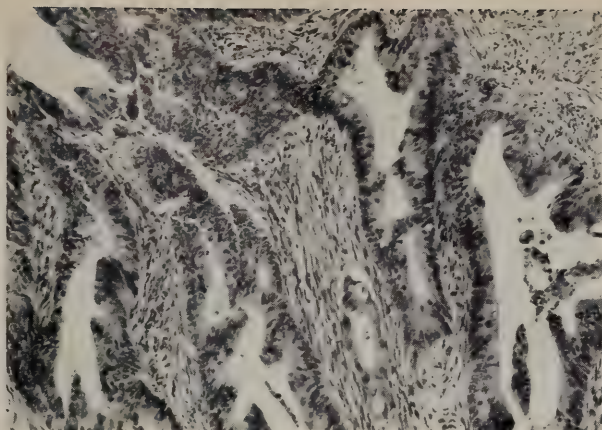


Figure 1.—Microphotograph of polypoid carcinoma of cecum. ($\times 400$)

Refer to: Ho L, Rosenman LD: Metastasis to one lymph node from two colonic carcinomas. *Calif Med* 116:85-86

Metastasis to One Lymph Node from Two Colonic Carcinomas

LIN HO, M.D., AND LEONARD D. ROSENMAN, M.D., *San Francisco*

MULTIPLE SYNCHRONOUS intestinal neoplasms are not rare. Lesions metastatic from them generally occur independently. The case here reported demonstrates an unusual and therefore interesting metastatic pattern. Metastasis to the same lymph node in the adjacent mesentery occurred from two separate but adjacent colonic carcinomas.

Report of a Case

A 68-year-old woman noted increasing tiredness for two months. She denied gastrointestinal symptoms and had recognized no blood at stool. General examination showed no abnormalities other than pallor. Results of laboratory studies showed hemoglobin of 8 grams per 100 ml; erythrocytes 3.9 million per cu mm; hematocrit 28 percent. A barium enema study revealed several lesions, sessile and polypoid, in the cecum and ascending colon.

Submitted June 1, 1971.

Reprint requests to: L. D. Rosenman, M.D., Department of Surgery, Mount Zion Hospital and Medical Center, 1600 Divisadero Street, San Francisco, Ca. 94115.

At laparotomy a fungating cecal tumor near the ileocecal valve was observed. It was 6 cm in diameter and protruded 2.5 cm into the lumen. Eight centimeters distal to that lesion, in the ascending colon, was a plaque of ulcerated tumor, 2.5 cm in diameter, causing induration of all layers. The mucosa between the two carcinomas contained two small (0.5 cm and 0.2 cm) benign polyps. One firm 1.5 cm lymph node lay in the mesentery adjacent to the more distal carcinoma. Several small soft lymph nodes were found in the remainder of the mesentery.

Microscopic examination demonstrated the cecal tumor to be a polypoid carcinoma penetrating only to the muscularis, composed of proliferating glands of irregular and complex shapes lined by tall columnar cells (Figure 1). The second lesion was entirely ulcerative and endophytic, composed of solid nests of tumor cells, with small central spaces, the larger of which showed central necrosis. The morphologic pattern of this tumor (Figure 2) differed significantly from that of the cecal tumor, indicating it was a separate primary carcinoma.

The pattern of metastasis was unusual. The larger firm lymph node contained lesions metastatic from both the primary tumors (Figure 3). One of the small soft nodes had a single metastatic deposit resembling the polypoid lesion.

Discussion

Many observers¹⁻¹² have reported multiple malignant lesions of the intestine. The incidence is variously reported from 1.2 to 9 percent of all colonic cancers. Slaughter noted that multiple neoplasms occur more commonly in the gastro-

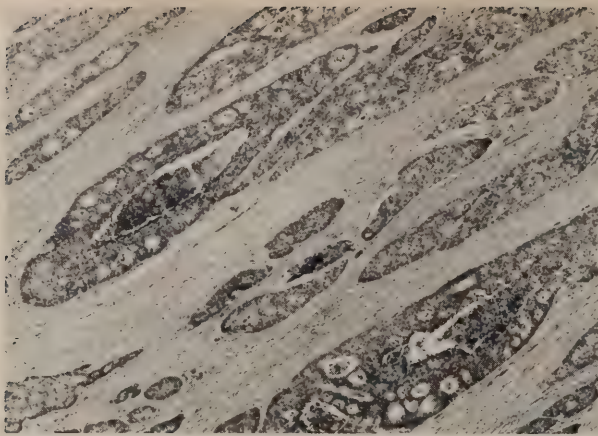


Figure 2.—Microphotograph of ulcerative carcinoma of ascending colon. ($\times 400$)

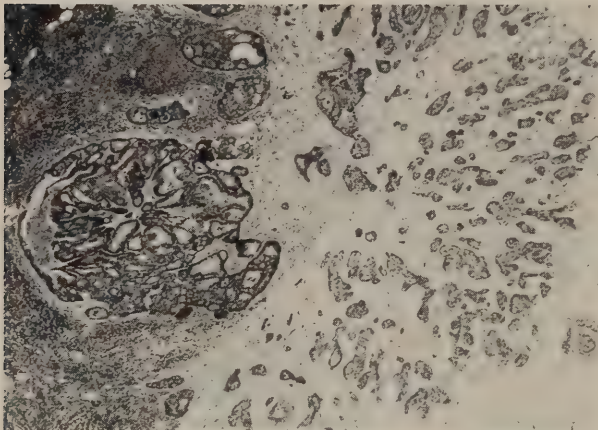


Figure 3.—Microphotograph of mesocolic lymph node with metastasis from both carcinomas. ($\times 400$)

intestinal tract than in other single organs. Moertel noted that often in such cases the primary lesions are close to each other.

The occasional metastasis of one tumor into another has been termed "collision."¹³ Although there are several reports of collision metastasis¹³⁻¹⁵ we find no report of a case similar to this one, in which there was metastasis to a single lymph node from two primary carcinomas.

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Refer to: Knapp WA, Seeley TT, Ruebner, BH: Fatal coccidioidomycosis—Report of two cases. *Calif Med* 116:86-90, Mar 1972

Fatal Coccidioidomycosis

Report of Two Cases

WILLIAM A. KNAPP, M.D., AND
THOMAS T. SEELEY, M.D., *Sacramento*,
AND BORIS H. RUEBNER, M.D., *Davis*

The presence of coccidioidomycosis in the dry Southwestern part of the United States and in Northern Mexico has been known since 1896.¹ In 1969, California reported 349 infections while Arizona reported 537. The mortality in the United States averages 53 cases per year.² The disease is also endemic in South America and in sections of Central America. In California it is endemic in the southern part of the Central Valley, especially the San Joaquin Valley near Bakersfield.³ Recently, cases have been reported from certain areas of the northern Central Valley.⁴ Whether this expansion of the endemic area represents a wider dissemination of *Coccidioides immitis* or increased clinicopathological awareness is not known.

The clinical presentation and the pathologic changes of the human infection caused by *Coccidioides immitis* have been well documented. At this hospital, we have recently encountered

From the Department of Pathology, Sacramento Medical Center, and the University of California, Davis, School of Medicine.

Submitted May 31, 1971.

Reprint requests to: W. A. Knapp, M.D., Department of Pathology, Sacramento Medical Center, 2315 Stockton Boulevard, Sacramento, Ca. 95817.

two fatal cases of coccidioidomycosis. The clinical manifestations were as strikingly different as the pathological findings. The ability of this infection to mimic a wide spectrum of diseases is remarkable. An important lesson to be learned from these two cases is to include coccidioidomycosis in the differential diagnosis of obscure respiratory disease and of chronic disease of uncertain cause. This is especially important in "fringe endemic areas" and in non-endemic areas where the infrequency of cases may predispose to diagnostic errors.

Reports of Cases

Case 1. A 54-year-old white man was admitted to another hospital 8 September 1970 because of a two-week history of hematemesis and melena. A diagnosis of impending hepatic coma and an upper gastrointestinal hemorrhage, possibly from esophageal varices, was made. The patient was transferred to the Sacramento Medical Center for further evaluation and treatment. On physical examination the patient appeared to be in moderate distress. He was minimally jaundiced, had a moderate amount of ascites, and had pitting edema to the midcalves bilaterally. Spider angiomas were present over the upper chest anteriorly. Clinical and laboratory investigations substantiated the diagnosis of impending hepatic coma and probable esophageal varices. Chest radiography demonstrated a diffuse pattern of minimal interstitial fibrosis. No areas of consolidation were present. Therapy aimed at prehepatic coma resulted in improvement of the sensorium. No further upper gastrointestinal hemorrhage developed. The patient felt improved and signed out of the hospital against medical advice on September 12. Two days later he was readmitted because of briskly bleeding hemorrhoids. On the second hospital day acute peritoneal signs developed and emergency celiotomy was performed. A perforated anterior duodenal ulcer was oversewn, primarily. The patient did poorly postoperatively. The major problem was respiratory failure that clinically and by radiography consisted of a nearly confluent bilateral lower lobe and right middle lobe bronchopneumonia. Part of this complication was attributed to aspiration of vomitus during induction of anesthesia. The patient's respiratory status deteriorated over the next 48 hours and he died September 23.

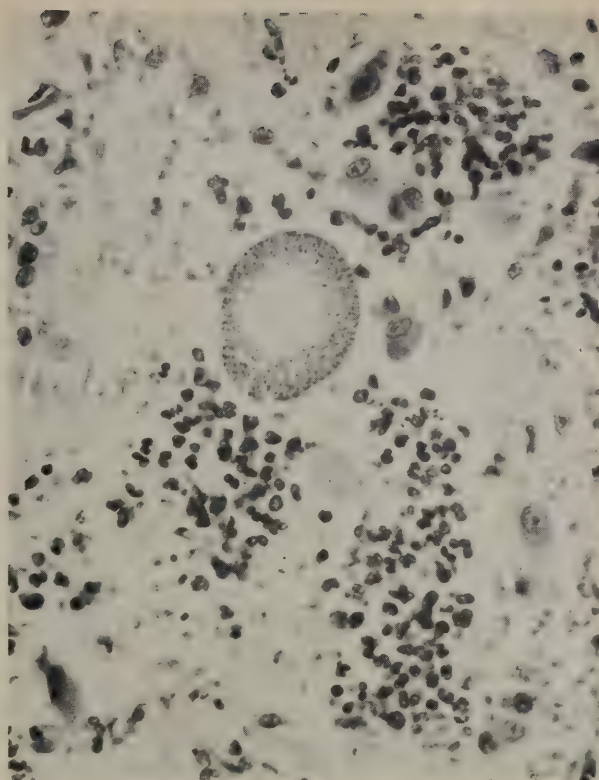


Figure 1—Case 1.—Lung. Spherule of *Coccidioides immitis* with polymorphonuclear infiltrate of acute exudative pneumonia. (Hematoxylin and eosin stain, $\times 425$.)

Pathologist's report: At autopsy, severe edema and consolidation in the lungs was observed. The right lung weighed 1,880 grams, the left weighed 1,500 grams, and there was no evidence of aspiration of vomitus. The liver was finely nodular and weighed 1,940 grams. The spleen was fibrotic and weighed 200 grams. Esophageal varices were present but there was no evidence of recent bleeding. An anterior duodenal ulcer had been oversewn. Organizing peritonitis was extensive.

Microscopic examination of the lungs revealed an acute exudative pneumonia with pronounced polymorphonuclear leukocytic infiltrate. The agent responsible for this fulminant, fatal pneumonia was identified histologically as *Coccidioides immitis* (Figure 1). Periodic Acid-Schiff (PAS) and silver methenamine stains were positive and demonstrated coccidioidal spherules in alveoli and terminal bronchioles in all lobes of both lungs. There was no evidence of chronic, granulomatous pulmonary coccidioidomycosis or coccidioidal involvement of other organs. Micronodular cirrhosis with extensive necrosis affecting the centers of the nodules was the cause



Figure 2—Case 2.—1968 liver biopsy showing granuloma with spherules of *C. Immitis*. (PAS stain, $\times 350$.)

of liver failure. The remaining viable hepatocytes contained alcoholic hyaline and showed fatty change.

Case 2. A 49-year-old white man was admitted to Sacramento Medical Center on October 30, 1970 with chief complaint of light-headedness when standing. Also, since 1968 he had dyspnea of increasing severity. A diagnosis of systemic sarcoidosis had been made in 1968 at another hospital to which he had been admitted for evaluation of respiratory complaints. Evidence for that diagnosis included a work up completely negative for tuberculosis, chest roentgenograms compatible with sarcoidosis, and a liver biopsy which showed scattered noncaseating granulomas. No acid-fast bacilli or fungi were identified in the liver biopsy at that time but review of the original sections after the patient's death revealed spherules typical of *Coccidioides immitis* (Figure 2). Isoniazid had been given for one year with little or no improvement in respiratory symptoms. Subsequently, this patient attended the Sacramento Medical Center as an outpatient for management of mild onset diabetes.

On physical examination at the time of admission the patient appeared chronically ill. Orthostatic hypotension was found, with blood pressures as follows: reclining, both arms 110/60 mm of mercury; standing, both arms 80/50 mm. The skin was dry and the areolae and mucous membranes hyperpigmented. Examination of the chest revealed no consolidation and very distant breath sounds were heard bilaterally. No abnormality was noted on examination of the abdomen and no symptoms referable to the central nervous system were detected.

Serial radiography of the chest showed a progressive nodular infiltrate that involved all lobes of the lungs. The pattern was thought compatible with progressive miliary tuberculosis or pulmonary carcinomatosis. Absence of adrenal cortical function was documented by 24-hour urine assays for 17-ketosteroids and 17-ketogenic steroids with values of 3.3 mg and 1.8 mg respectively. There was no adrenal cortical response to exogenous ACTH. Liver biopsy showed no granulomas and was reported as normal. After the patient's death, step sectioning of the biopsy specimen showed non-caseating granulomas but no coccidioidal spherules. Results of skin tests for tuberculosis and coccidioidomycosis were negative. Complement fixation studies for *C. immitis* were not done.

The patient's condition worsened progressively during his stay in hospital. Isoniazid therapy was reinstituted and replacement steroids were administered because of his hypoadrenal cortical state. The cerebrospinal fluid contained 400 leukocytes per cu mm with 90 percent polymorphonuclear leukocytes. The protein content was 133 mg and the glucose content 20 mg per 100 ml. Blood sugar of 200 mg per 100 ml. No acid-fast bacilli, fungi or bacteria were seen in the smears. The patient died on 12-1-70.

Pathologist's report: The right lung weighed 750 grams, the left lung 600 grams. They were diffusely infiltrated by hard, gray nodules averaging 1 to 2 mm in diameter. The adrenal glands were enlarged and weighed 80 grams each. On cross-section they appeared to be completely replaced by bulky, whitish yellow material. The liver was grossly normal. The pia-arachnoid covering the brain stem was boggy, edematous, and involved by a purulent process. No similar involvement was seen over the convexities of the cerebral hemispheres.



Figure 3—Case 2.—Kidney. Spherules of *C. immitis* in venal tubules. Acute to chronic inflammation is also present. (Hematoxylin and eosin stain, $\times 190$.)

Microscopic examination demonstrated widely disseminated non-caseating granulomas in lungs, liver, thyroid gland, heart, lymph nodes, and kidneys. Microorganisms morphologically characteristic of *Coccidioides immitis* could be identified in all of these except heart and thyroid gland. In the kidney, spherules were seen in medullary tubules (Figure 3). The adrenal glands had been totally replaced by caseous granulomas. The inflammatory cells infiltrating the basal meninges consisted of equal numbers of polymorphonuclear leukocytes and mononuclear inflammatory cells. Many spherules could be seen among the inflammatory cells. A culture was positive for *C. immitis*.

Discussion

The first patient's course was very acute; he lived only a few days, and the correct diagnosis was not considered. This emphasizes the existence of an acute, pneumonic form of the disease which is potentially fatal. A sputum smear was not examined during his second admission. This investigation might have been diagnostic because

of the many coccidioidal spherules seen in alveoli and in terminal bronchioles. However, because of the severe liver disease and poor general condition of the patient, it seems unlikely that therapy at this stage would have been beneficial.

The second case illustrates the chronic and disseminated form of coccidioidomycosis. The diagnosis of coccidioidomycosis was considered during a period in hospital in 1968. Although spherules were observed on liver biopsy the diagnosis was missed, probably because the spherules were PAS negative (Figure 2). It has been shown that the silver methenamine method stains a larger percentage of coccidioidal spherules positively than the PAS method.⁵ During the final period in hospital the correct diagnosis was again considered but could not be substantiated. Skin tests were negative, probably because of the anergy that usually accompanies disseminated infection by *C. immitis*.⁶ Complement fixation tests were not done, but probably would have confirmed the diagnosis. A liver biopsy showed no granulomas. Step sectioning of the liver specimen would have demonstrated granulomas. The finding of *C. immitis* within renal tubules at autopsy suggests that diagnosis by urinalysis or urine culture might have been possible.

Successful treatment of acute and chronic coccidioidal infections with amphotericin B is possible. Early diagnosis therefore is extremely important. The two cases described here were not diagnosed during life perhaps because they had some atypical features. Both patients were white. Most cases of disseminated coccidioidomycosis occur in non-whites although the overall incidence of primary infection is probably not different among various races.⁷ The first patient had alcoholic cirrhosis which may have predisposed him to the fatal pneumonic form of coccidioidomycosis. In the second patient classical Addison's disease developed. While adrenal gland involvement by *C. immitis* is not rare, the production of this clinical picture is extremely uncommon.⁸ This is one of the reasons why the diagnosis of tuberculosis was so strongly considered in this case.

Although both patients were seen in hospitals immediately adjacent to the historically endemic area of the San Joaquin Valley, the correct diagnosis was not made. Greater awareness of the possibility of this disease would surely decrease

its mortality in "fringe endemic areas" as well as in non-endemic areas where the incidence of the disease seems likely to rise because of increased travel.

Summary

The development of effective therapy has made the diagnosis of coccidioidomycosis very important. The first patient was an alcoholic with severe liver disease who developed the acute pneumonic form of the disease. This case points out the importance of a thorough study of the sputum for fungi in pneumonias of uncertain etiology. The second patient suffered from chronic granulomatous coccidioidomycosis and finally developed adrenal failure and meningitis. When a definitive diagnosis of tuberculosis cannot be made in such patients further studies such as a complement fixation test for coccidioidomy-

cosis, step sectioning of a liver biopsy stained with methenamine silver and study of the urine for fungus are indicated. It is pointed out that coccidioidomycosis will occasionally be seen outside of the classical endemic areas.

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BILIRUBIN DANGER IN THE NEWBORN

At any phase of bilirubin accumulation in the newborn there is a spectrum of damage to the nervous system. We must try to minimize that damage and thus treat infants *while* they accumulate bilirubin. This means seeing that infants who are becoming icteric are kept warm, quite warm, so that they do not break down fat in the body stores and thus have to transport free fatty acids from these stores to the liver for combustion. We know that free fatty acids interfere with the binding of bilirubin to albumin and will unfavorably influence the distribution of bilirubin. Keeping an infant warm who is becoming jaundiced is clearly a measure to minimize damage to the nervous system. We try to keep infants on adequate feedings so that they do not need to draw on their fat stores to remain alive. Feeding an infant generously, paying special attention to his water and caloric intake during the period of bilirubin accumulation, is another measure to minimize bilirubin damage.

We pay close attention to the carrier of bilirubin—albumin. We are concerned not only about the total level of albumin but whether there are any competing substances which will interfere with bilirubin. I mentioned free fatty acids; drugs must be mentioned here, sulfonamides notably. We're concerned about the acid-base state of the infant because his hydrogen ion concentration increases. The albumin bilirubin bond is threatened, and the likelihood of free diffusible bilirubin damaging the nervous system is thus increased.

We're concerned about the acid-base state, albumin, the infant's state of nutrition, and about his water intake; all of these measures must be carefully attended to as the infant becomes jaundiced.

—WILLIAM A. SILVERMAN, M.D., San Francisco
Extracted from *Audio-Digest Pediatrics*, Vol. 17, No. 7, in the Audio-Digest Foundation's subscription series of tape-recorded programs. For subscription information: 1930 Wilshire Blvd., Suite 700, Los Angeles, Ca. 90057

LETTERS *to the Editor*

such as the American Cancer Society and the California Medical Association because of the respect they command and the influence they exert must take the lead in avoiding this kind of implied discrimination.

RUTH A. PICK, M.D.

*Assistant Professor of Radiology
Council Member,
Professional Women of Stanford Medical School*

1 1 1

"The Liberated Sex"— Catchy, or Pejorative?

To the Editor: Recently I received in the mail a notice for a symposium entitled "Pelvic Cancer in the Liberated Sex" co-sponsored by the American Cancer Society and the California Medical Association. I am delighted that such a program is being provided for the physicians practicing in the greater San Francisco area; however, it is distressing that a symposium on such important subjects as uterine and ovarian cancer should be introduced with the flippancy and the inherent, subtle put-down that is implied in the term "liberated sex."

I have shown the announcement to many colleagues both male and female, as well as many other professional and nonprofessional people and uniformly they have reacted with as much distaste and irritation as I have. All asked "now what is that supposed to mean?" All felt the title reflects a lack of sensitivity to and understanding of the changes occurring in our society. You should no more talk about pelvic cancer in the "liberated sex" than you would talk about sickle cell anemia in the "jive race." Inherent in both of these expressions is the kind of subtle and (presumably) unintentional, implied but unstated prejudice which is the most difficult to combat because it is so insidious. Organizations

Dear Dr. Pick: Thank you for your letter concerning the title of the symposium on female pelvic cancer. We appreciate your very honest comments.

On behalf of the planning committee, I would like to assure you that the use of the term "The Liberated Sex" was not intended to be offensive or to indicate lack of our respect for women.

Often the title of an excellent program is so unimaginative that it does not receive more than a first glance. Our primary purpose for selecting this title was to attract attention and stimulate interest.

We regret that this has caused you concern and we will try to avoid any possibility of similar misinterpretations in the future.

VICTOR RICHARDS, M.D.

*Chairman, Planning Committee
California Medical Association/
American Cancer Society
Cancer Symposium
San Francisco*

Use of the Water Bed

To the Editor: I read the brief summary of the use of the water bed in the January, 1972, issue [Important Advances in Clinical Medicine:

Epitomes of Progress — Plastic Surgery]. Since you note "Clinical data is accumulating . . ." and "The water bed represents an important advance in the care of patients with paraplegia, stroke, spinal cord injury, and geriatric problems," I send you the following which I found in *Miss Beecher's Domestic Receipt Book* published in 1846 (Tenth Edition, 1852).

M. E. MOTTAM, M.D.
San Francisco

The drawing at Fig. 5 represents a contrivance for the sick, which ought to be prepared in every village, to rent out to those who need it.

Fig. 5.



It is called the *Water Bed*, or *Hydrostatic Couch*, and is made at an expense of from twelve to fifteen dollars. The object of it is to relieve the sufferings of those who, from extreme emaciation, or from ulcers, or bed sores, are great sufferers from the pressure of the bed on these sore places. This kind of bed proves a great relief from this kind of suffering.

It consists of a wooden box, six feet long, and two feet and a half wide at the top, and the sides gradually sloping inward, making it fourteen inches deep. This is lined with sheet zinc, to make it water tight. Over this is thrown, and fastened to the edge of the box, a sheet of thick India rubber, water-proof cloth, large enough for *an entire lining* to the inside of the box. The edges of it are first made to adhere to the upper edge of the box with spirit varnish, and then a thin strip of board is nailed on, to fasten it firmly, and make it water tight. Near the bottom, at A, is a hole and plug, to let off water; and at B, a tin tube, soldered in the upper part of the outside, to pour water in. When used, the box is to be filled half full of water, about blood warmth. Then a woollen blanket and pillow are laid upon the India rubber cloth, and the patient laid on them, and he will float as he would in water, and there will be no pressure on any part of the body greater than is felt when the body is in water.

This is important for all who suffer from bed sores, or sloughing in protracted fevers, from diseases in the hip-joint, from diseases of the spine, lingering consumption, and all diseases that compel to a protracted recumbent position. None but those who have seen, or experienced the relief and comfort secured to sufferers by this bed, can conceive of its value. The writer saw the case of a young man, who was enduring indescribable tortures with the most dreadful ulcers all over his body, and who had for several days and nights been unable to sleep, from extreme suffering. This bed was made for him, as an experiment, after trying every other mode of relief in vain. It was placed by his bedside, and the water poured in, and then his friends raised him with the greatest care in a blanket, and laid him on it. Instantly his groans ceased, an expression of relief and delight stole over his countenance, and exhausted nature sunk instantly into the most peaceful and protracted slumbers. And ever after, he was relieved from his former sufferings. Every hospital, every alms-house, and every village should have the means of obtaining such a bed for the many classes of sufferers who would thus find relief, and it is *woman* who should interest herself to secure such a comfort for the sick, who especially are commended to her benevolent ministries.

Equal Opportunity

To the Editor: The very essence of the scientific approach to life is to question, to demand proof, to require evidence, to be critical of, in other words, absolute freedom of speech. Without this approach, one tends to accept dogma, authority and tradition.

Modern medicine owes its effective knowledge and techniques to the scientific method. Modern medicine has arisen out of the superstition and witchcraft of the past.

It is the duty of all doctors to assist and develop the scientific method.

Yet there are publications such as the *Journal of the American Medical Association*, the *California Medical Journal* and the *Bulletin of the Sacramento Society for Medical Improvement*, which deny freedom of expression to those members who are critical of the policy of these organizations.

It is my contention that these publications ought to allow freedom of speech to all members, not just a select few. Any contribution by any member of the medical association ought to be welcomed and particularly those which are critical of the actions or policies of the organization. Any organization does not gain strength through idle flattery, but rather through the free action of free men.

In an organization where the dues and assessments are equal, the rights and privileges ought to be equal.

It is conceivable, nay it is probable, that the novelty of and the sudden confrontation with this concept of freedom of speech for each ordinary dues paying doctor may be so alarming to our inbred medical hierarchy that all kinds of terrible specters will be conjectured to abort such an idea. One such objection may be that to allow all members full freedom to use the columns of the journals will lead to their inundation with innumerable contributions necessitating new funds for expansion. To this I have two answers: (1) I doubt if there is enough interest or originality left in most physicians to

elicit very much of a response. (2) The medical organizations mentioned, which assess their members so much and give so little in return, could at least allow the doctors to be heard in the publications of their organizations. One could consider curtailing a regular column on gourmet eating or the history of medicine to allow a little democracy in the organization.

Sincerely,

JOHN E. SUMMERS, M.D.
Sacramento

EDITOR'S NOTE: This section of CALIFORNIA MEDICINE seeks to reflect the opinions of our readers. There are 27,000 of them. Therefore, of necessity some attention is given to both the quantity and quality of what can be published.

—MSMW

Doppler Monitoring

To the Editor: In *Epitomes of Progress—Plastic Surgery* [January, 1972], Kaplan and Vistnes¹ point out some of the many valuable uses to which Doppler ultrasound flowmeters can be put in clinical medicine. Although their concern was for use in plastic surgery, it brings to mind another application which has proved to be life-saving.

Certain types of surgical procedures place patients in greater risk of venous air embolism, with potentially catastrophic results if it is not rapidly

diagnosed and treated — particularly, posterior fossa operations in the sitting position, as well as some gynecologic and urologic procedures, pose such dangers.

Martin² and later Gronert and Michenfelder³ have described a technique for using the fetal Doppler flowmeter to monitor the heart of patients undergoing such procedures, and have found it to be very satisfactory in detecting tiny emboli of one to two milliliters volume. Combining such careful monitoring with preoperative placement of a right atrial catheter, and other precautions, has enabled these workers to treat rapidly and effectively such episodes without resort to the traditional measures. One need think only a moment of the difficulties of disengaging a patient from drapes and headrest during a craniotomy in order to lay him down and turn him on his side, and do it fast, to recognize the virtues of a system that seems to remove the need for such gyrations.

There appears to be only one major disadvantage to continuous Doppler monitoring—the sounds produced are loud and continuous, and are, therefore, potentially quite irksome to the entire operating team.

FRANK W. SETCHELL
*Assistant Editor, Anesthesiology
Audio-Digest Foundation*

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EYE DROPS FOR THE EARS

I don't think there are any otitic steroid solutions that are steroids alone; they all are in combination with an antibiotic. So when I have an ear canal that is markedly pruritic and has no other problems (the patient just has severe itching and nothing else manages it) I prescribe a steroid eye drop. You can order eye drops and underline the word "ears." The pharmacist will be on the phone in 30 seconds asking whether you really want to put the drops in the ear; but that's what I use.

—ALLEN M. DEKELBOUM, M.D., San Francisco
Extracted from *Audio-Digest Otorhinolaryngology*, Vol. 3, No. 2, in the Audio-Digest Foundation's subscription series of tape-recorded programs. For subscription information: 1930 Wilshire Blvd., Suite 700, Los Angeles, Ca. 90057

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Special Article

Marital Stability Among Physicians

K. DANIEL ROSE, A.B., AND IRVING ROSOW, PH.D., *San Francisco*

■ *Analysis of 57,514 initial complaints for divorce, separate maintenance, and annulment filed in California during the first six months of 1968 reveals that physicians are considerably less prone to marital failure than men of comparable age in the general population. Furthermore, when compared to professionals in general, doctors also appear less prone to marital collapse. For physicians, marriages break down in the greatest numbers and at the greatest rate between the ages of 35 and 44. Women doctors are at least 40% more prone to marital instability than men, and black physicians are nearly 70% more prone to divorce than their white colleagues. Of the individual specialists, orthopedists and psychiatrists possibly have the highest rates of marital demise.*

THE LATE LOUIS DUBLIN OF METROPOLITAN LIFE proposed that divorce is common in occupations with irregular hours, absence from home at night, and frequent, unchaperoned contact with members of the opposite sex.¹ He suggested that "actors, traveling salesmen, musicians, military personnel, seamen, and physicians appear to have more than their share of divorces." Indeed, many physicians likewise believe that divorce occurs frequently within the profession.

A search of the divorce literature neither confirms nor disproves this commonly held notion about physicians. In fact, no studies of physi-

cian divorce are to be found. It is the purpose of this investigation to assess the level of marital instability among physicians and to describe the characteristics of those whose marriages fail.

Materials and Method

For this study, an unstable marriage is defined as one in which husband or wife files an initial complaint for divorce, separate maintenance, or annulment. It matters not whether this legal action terminates in final decree. The mere filing of the legal suit is taken to be sufficient indication of significant marital strife.

Our results are based on all the initial complaints for divorce, separate maintenance, and annulment filed in California during the first six months of 1968. These materials were prepared from special computer runs for this study at the Bureau of Health Intelligence, California De-

At the time of writing this report Mr. Rose was a fourth year medical student, University of California, San Francisco; Dr. Rosow is from the Langley Porter Neuropsychiatric Institute, University of California, San Francisco.

This study was supported in part by General Research Support Grant FR 69-49 from the Langley Porter Neuropsychiatric Institute.

Submitted September 14, 1971.

Reprint requests to: Mr. K. Daniel Rose, 717 Laurelwood Dr., San Mateo, Ca. 94403.

TABLE 1.—*Initial Complaint Rates for Married Male Physicians, and for Californians as a Whole, by Age, 1968*

Age Group	Physicians			Californians		
	Init Comp	Married Pop*	Annual Rate†	Init Comp	Married Pop‡	Annual Rate†
25-34‡	48	5,710	16.8	20,203	996,200	40.6
35-44	105	9,610	21.9	14,115	1,049,700	26.9
45-64	86	12,622	13.6	10,724	1,606,700	13.3
65 & over	8	3,220	5.0	736	507,900	2.9
Unknown	2			1,271		
TOTAL	249	31,162	16.0	47,049	4,160,500	22.6

†Per 1000 population.

*Calculated by applying the proportion married in each age group of male MD's in the U.S., 1960 (Source: U.S. Bureau of the Census, U.S. Census of Population: 1960, Subject Reports, Characteristics of Professional Workers, Final Report PC (2)-7E, Government Printing Office, Washington, DC, 1964, Table 3), to the population in each age group in California, Dec 31, 1967 (Source: American Medical Association, Selected Characteristics of the Physician Population, 1963 and 1967, Chicago, 1968, Table 31).

‡Calculated by applying the proportion married in each age group of men in California, 1960 (Source: U.S. Bureau of the Census, U.S. Census of Population: 1960, Vol 1, Part 6, Washington, DC, 1963, Table 105), to the population in each age group in California, July 1, 1968 (Source: California Department of Finance, Sacramento, on request.).

†Includes some physicians under age 25.

partment of Public Health.* They include detailed demographic information on the physicians and other professionals involved in initial complaints.

Since the number of initial complaints filed between January and June equals the number filed between July and December, annual complaint rates may be calculated by doubling the six-month figures.² Each complaint involves a man and a woman, both of whom may be physicians. Hence, it is more correct to think in terms of the number of MD's involved in initial complaints rather than the total number of complaints involving MD's.

Annual rates of initial complaint are computed for married populations when census figures allow. These are the rates of marital instability—the reflection of “proneness to divorce.” Of course, marital satisfaction is not necessarily equivalent to marital stability, since unhappy marriages do not always culminate in divorce.

Age adjusted complaint rates are calculated for only a few groups due to the lack of adequately detailed population figures. Since divorce rates in California are higher than for the nation as a whole, our analysis focuses on patterns of marital instability within the state. In 1968, for example, crude rates per 1000 population were 3.9 for California and 2.9 for the United States.³

*We are indebted to Harry Greenblatt and Robert Mielke, social research analysts, of the Bureau of Health Intelligence for their generous cooperation in compiling these data.

Results

In the period under study, 57,514 initial complaints were filed in California, involving 115,028 men and women. These include 3,403 persons in one or another of the professions, of whom 267 are physicians. The notion that physicians are divorce-prone appears to be completely without basis. In fact, male MD's are considerably less proclived to marital disruption than a comparable group of married men in the general population. It can be seen from Table 1 that the rate of marital instability, on the average, is 41 percent higher in the general population than it is among physicians, the difference being concentrated before age 45. Compared with the age-adjusted rate for physicians—15.4—the initial complaint rate for the general population is 47 percent higher (age-adjusted by the direct method using the married male California population as the standard).

Compared with other professional people—persons of similar age, status, education, and income—physicians also appear to be less prone to divorce. It can be seen from Table 2 that the initial complaint rate for physicians is lower than the average for professional people and lower than the rates for most individual professions as well.

Although physicians as a group do not appear to be divorce-prone, certain subgroups within the medical profession do exhibit varying degrees of marital instability. Initial complaint data have

TABLE 2.—Initial Complaint Rates of Married California Professionals, 1968

Professionists†	# Involved in Initial Compl Jan-June 1968	Married Population Size, 1968*	Annual Rate of Complaint #/1000/Year
Authors	102	6,969	29.3
Social Scientists	79	5,572+	28.4
Architects	53	3,972+	26.7
College Faculty, Admin	184	18,250	20.2
Lawyers, Judges	240	24,679+	19.5
Engineers	1,593	172,003	18.5
Chemists	57	6,614+	17.2
Editors, Reporters	92	11,028	16.7
Dentists	87	10,558+	16.5
Accountants, Auditors	538	65,176	16.5
PHYSICIANS	267	32,526+	16.4
Natural Scientists	116	14,399+	16.1
TOTAL	3,408	371,746	18.3

†Category as defined by California Department of Public Health.

*Calculated by applying the proportion married in each occupation in the U.S., 1960, (Source: see second footnote to Table 1) to the population in each occupation in California, 1968. The latter were obtained from professional societies and State licensing boards (marked by +) or estimated by increasing the 1960 Census figures for California by 63.6% (the amount the "known" groups had increased between 1960-1968).

been compiled for physicians of different age, sex, race, and specialty area. With these data one can describe the characteristics of physicians whose marriages are most likely to fail.

The crisis period in physician marriage most commonly occurs at the height of one's medical career. This can be seen in Table 1, which shows that the greatest number of MD marriages collapse between the ages of 35 and 44. This is also the period during which the rate of marital failure is the highest. Up to this decade in life, dissolution of marriage occurs less commonly and at a much lower rate. Thus, any notions about a rash or divorces occurring just after internship and residency are simply incorrect. The peak of initial complaint activity is a full ten years beyond the training period. After age 44, the rate of marital instability declines rapidly.

The propensity to divorce is 48 percent greater for women physicians than for men, and the crude rates are presented in Table 3. A comparison of age-adjusted rates reveals that women are 43 percent more liable to marital breakdown than male physicians (23.9 to 16.7 using the married California female MD population* as the

TABLE 3.—Initial Complaint Rates of Married California Physicians, by Sex, 1968

	# Involved in Initial Compl Jan-June 1968	Married Population Size, 1968*	Annual Rate of Complaint #/1000/Year
Men	249	30,951	16.1
Women	18	1,505	23.9
TOTAL	267	32,456	16.4

*Calculated by applying the proportion married in each sex of U.S. physicians, 1960, to the population of each sex in California, 1968. (Sources: see second footnote to Table 1.) These figures vary slightly from those in Tables 1 and 2 because the age and sex distributions of California doctors differ somewhat from those of U.S. physicians. The variance, however, is less than 1%, and the effect on rates is negligible.

TABLE 4.—Initial Complaint Rates of California Physicians, by Race, 1968

Race	# Involved in Initial Compl Jan-June 1968	Population Size, 1968*	Annual Rate of Complaint #/1000/Year
White	251	35,682	14.1
Black	7	574	24.4
Other Nonwhite	7	964	14.5
Unknown	2		
TOTAL	267	37,220	14.3

*In the absence of better data, the 1968 figures were estimated using the racial distributions at the time of the 1960 Census. Source: U.S. Department of Commerce, Bureau of the Census: U.S. Census of Population, 1960. Vol 1, Part 6, Washington, DC, Government Printing Office, 1963. Table 122, pages 696 and 698.

standard). Marital failure occurs at the same time, the mean age at complaint being 43.1 years for both men and women. That women in medicine tend to avoid marriage is clear from the national figures, which show 31 percent of women physicians never married compared with only 8 percent of men.*

Marital instability among physicians of different races varies widely. As can be seen in Table 4, the initial complaint rate for black doctors is more than 70 percent higher than for their white colleagues. Other non-white MD's do not differ substantially from whites in tendency to divorce. Although the 95 percent confidence interval (around the 7 observed cases) includes a rate as low as 9.8 for Blacks, the coherence of the observed finding with existing research indicates that its general magnitude is probably valid.^{4,5} It is not clear what, if any, difference between white and black rates is accounted for by differing age or marital composition of the two groups. Adequately detailed census figures for this comparison are not available. For the time being, however, it is reasonable to accept the

*Source: see second footnote to Table 1.

TABLE 5.—Initial Complaint Rates of California Physicians by Medical Specialty, 1968

Specialties*	# Involved in Initial Compl Jan-June 1968	Population Size, 1968†	Annual Rate of Complaint #/1000/Year
Orthopedic Surgery	14	1,237	22.6
Psychiatry	26	2,724	19.1
Dermatology	5	560	17.9
General Practice	68	8,182	16.6
Physical Med & Rehab	1	126	15.9
Ophthalmology	9	1,131	15.9
Neurology	2	255	15.7
Administrative Med	3	406	14.8
Obstetrics & Gynecology	15	2,085	14.4
Pediatrics	15	2,079	14.4
General Surgery	20	2,981	13.4
Radiology	9	1,391	12.9
Surgical Subspecialties‡	5	811	12.3
Otolaryngology	4	659	12.1
Internal Medicine	28	4,983	11.2
Urology	3	698	8.6
Medical Subspecialties§	2	523	7.7
Anesthesiology	4	1,451	5.5
Pathology	2	950	4.2
Preventive Med¶	1	594	3.3
Unknown, Inactive	31	3,394	18.3
TOTAL	267	37,220	14.3

*All groupings follow the specialty classifications of the American Medical Association except for the arbitrary combination of the four small surgical subspecialties noted. Source: American Medical Association: American Medical Directory, 24th edition. Chicago, 1967. page xiii.

†December 31, 1967. Source: American Medical Association: Selected Characteristics of the Physician Population, 1963 and 1967. Chicago, 1968. Table 23, pages 167-168.

‡Surgical: Plastic, Neurosurgery, Colon and Rectal, Thoracic.

§Medical: Allergy, Cardiovascular, Gastroenterology, Pulmonary.

¶Preventive: General, Aviation, Occupational, Public Health.

preliminary finding that black physicians are considerably more prone to marital instability than whites.

Initial complaint rates for the various specialty areas are presented in Table 5. No adjustment of the rates is possible due to the lack of age, race, and sex data for each specialty. Although orthopedists and psychiatrists appear to have the highest rates of marital instability, firm conclusions along this line are unwarranted. Chi square testing indicates a substantial possibility that the results observed in Table 5 are due strictly to chance (chi square significant at a level of

$P=0.3$). If one reorganizes all the specialties along the classical "medical" and "surgical" lines, no considerable difference in propensity to divorce can be observed. The initial complaint rates for the medical and surgical specialties thus constructed are 14.2 and 13.4 respectively.

Discussion

Marital stability is the rule rather than the exception among physicians. Although certain sub-groups of physicians exhibit an increased risk of marital collapse, as a whole they cannot be characterized in the way Dublin has suggested. Actually, this finding is not surprising, for Udry and Kephart have clearly shown that divorce occurs less frequently among persons of higher income, education, and social standing.^{4,5,6}

In fact, we have gone a step further by looking at individual occupations. Even when compared with persons of similar class, physicians still demonstrate a decreased propensity to marital breakdown. If there are excessive or unusual stresses attendant to the practice of medicine, they are not evidenced by a high rate of physician divorce.

One of the major problems in epidemiologic research such as this is the lack of adequately detailed population statistics for physicians. U.S. Census figures are somewhat limited in scope, and dependence on them inhibits the study of problems between census years. The Department of Survey Research of the American Medical Association would be an ideal clearinghouse for data on physicians and could facilitate the study of divorce and other problems within the medical profession.

Further investigation of national scope is needed before the problem of physician divorce can be properly considered. Patterns observed in California may not exist elsewhere, and this is important to test. Studies through time might evaluate the effects of changing work styles (brought about by group practice, national health insurance, etc.) on the stability of physicians' marriages.

In conclusion, we have developed strong evidence to support the view that, relatively, physicians have stable marriages. In raw numbers, physicians most commonly involved in initial complaints are those age 35 to 44, males, whites, and general practitioners. But physicians at

greatest risk include those age 35 to 44, women, Blacks, and, possibly, orthopedists. We have purposely avoided any discussion of the reasons for the observed findings. Analysis of the many complex sociological issues involved in each observation is beyond the scope of this article. Suffice it to say that the present data appear to clear the medical profession of the stigma of frequent marital failures.

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MANAGEMENT OF ABDOMINAL STAB WOUNDS

Do you explore all patients with stab wounds of the abdomen?

I personally do not although the rest of the people on our service at a city hospital do. Because of this I have had some occasion to see on a single surgical service the difference between these methods. . . . My approach to stab wounds involves so-called selective management. Essentially what this means is a history and physical examination done at the beginning and then repetitively. . . . I don't use any supplementary techniques like x-ray demonstration of the penetration. I decide primarily on the basis of the history and physical and careful observation. The reason is that the essence of the problem is not whether the object went through the peritoneal cavity, which is what the x-rays show, but whether it went through and did something I should do something about. For example, if you take liver injuries, 30 percent of those objectively demonstrated are not treated at the time of surgery. The surgeon looks and says, "Yes, isn't it interesting." No sutures are put in. . . . One can go through this in every circumstance and show that even in the series where intraperitoneal injury has been demonstrated by x-ray about 30 percent of people still have nothing done although they have some damage. . . .

What I am really saying then is that I think with careful physical examination, selective management of penetrating abdominal wounds is a policy worth considering. At least in my own experience in a place where others don't believe in this, I have no reason yet to regret making this decision.

—LESTER F. WILLIAMS, JR., M.D., Boston
Extracted from *Audio-Digest Surgery*, Vol. 18, No. 8, in the Audio-Digest Foundation's subscription series of tape-recorded programs. For subscription information: 1930 Wilshire Blvd., Suite 700, Los Angeles, Ca. 90057

The Health Maintenance Organization

Some Information for Physicians

A Report of the Bureau of Research and Planning,
California Medical Association

The so-called "Health Maintenance Organization" constitutes one of the greatest sources of confusion and misunderstanding among physicians of any recent development in the area of health care financing and delivery. This report attempts to answer some of the more important questions, as well as to provide current data concerning the situation within California.

An initial source of concern to physicians and others interested in health care is the fact that the Health Maintenance Organization has not been well defined, but rather has merely been described in terms of its functions. This apparent paradox is necessary, however, since the configuration of an individual Health Maintenance Organization can vary considerably as long as the HMO fulfills certain criteria. Functionally, it must be prepared to guarantee the following elements to a defined population:

1. Accessibility of services,
2. Availability of services,
3. Continuity of care,
4. Comprehensiveness of benefits.

Furthermore, services must be made available to the subscribing population through a prospective capitation payment of a negotiated amount (prepaid) per individual or family.

A problem of understanding immediately arises because of the fact that the term Health Maintenance Organization does not accurately describe the concept in its current form. Originally, it implied the presence of a broad spectrum of preventive services; thus, the application

of the term "maintenance." Now, however, the term is used to describe any operation which functions as outlined above. This does not necessitate the availability of preventive services although they may, in fact, be present.

Many Models May Fit the Mold

Another difficulty in understanding Health Maintenance Organizations relates to the variations in configuration through which services may be provided. Although the classic example of an HMO is based on the framework of a group practice with prepayment, the two forms of health care delivery are not interchangeable. Besides professional groups, organizations such as Foundations for Medical Care, hospitals, insurance carriers, non-professional corporations and other types of cooperative arrangements may also serve as a Health Maintenance Organization. The requirement is merely in terms of the services and the mode of subscriber payment, not necessarily the organizational structure. Nevertheless, two other objective states for HMO's are (1) to bring about greater organizational efficiency together with more effective control of quality of medical care; and (2) to control costs of care.

It should be emphasized that the method of payment to professionals is equally irrelevant. HMO's may remunerate participating physicians on a fee-for-service basis or any other basis that may be mutually acceptable. Additionally, various portions of the package of services offered to the public may be subcontracted. The requirement is merely that they be guaranteed.

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Contents of a package of services offered may vary according to each defined population group, but each "package" must be available to whatever other group desires to select it.

Enabling Legislation Still Pending

At this time no specific legislation has been enacted to provide funding for Health Maintenance Organizations. Nevertheless, three important pieces of legislation are pending nationally:

1. A portion of HR1, the Social Security Act of 1971, relating to the availability of an HMO option for Medicare patients;

2. The Administration-sponsored HMO Assistance Act, S1182 in the Senate and HR5615 in the House of Representatives, which would provide \$45 million for HMO grants and loans to plan and develop new HMO's, to expand existing ones and to aid in initial costs in underserved areas:

3. The Rogers-Roy Bill (HR11728), the Health Maintenance Organization Act of 1971, a more elaborately detailed package, consisting of various types of grants and loans for HMO planning, development, and initial operating costs.

As the concept of the HMO becomes questioned in more depth, both as a mode for providing services and in terms of its economic advantages, the chances of passage of such enabling legislation become less certain.

Existing Funds Being Used by HEW

In the absence of specific enabling legislation, however, existing sources of funds are being employed in order to encourage the conduct of feasibility studies as well as the development of HMO's. Developmental funding is being provided through Title 314e of the Comprehensive Health Planning Act. In addition, some limited funding for evaluation is being made available through that legislation. In California funds were made available in the early part of 1971 for four developmental projects, two of which are being sponsored by Foundations for Medical Care. These foundations are the Sacramento County Foundation and the Sonoma County Foundation, each of which is being funded in excess of \$100,000. The other two developmental projects are sponsored by the Lutheran Hospital Society and the Health Services Alliance of San Jose.

Applications for 1972 grants under comprehensive health planning recently received primary review for future funding. Sixteen such applications in California, with sponsorship from a variety of sources, were reviewed, including some submitted by hospitals, county medical societies, medical schools, group practices, insurance carriers and a combination of various types of agencies. In the latter part of December, the following six grant proposals in California were approved for funding for 1972: Contra Costa Medical Services, Martinez, \$101,000; Health Services Alliance of San Jose, Inc., \$31,500 to supplement its 1971 initial grant of \$102,000; John Hale Medical Society, San Francisco, \$25,000 for a feasibility study; St. Joseph's Hospital, San Francisco, \$25,000 for a feasibility study; a coalition of the San Francisco Medical Society and the University of California, San Francisco, \$156,349; and Watts Extended Care Inc. (sponsored by the Charles R. Drew Postgraduate Medical School), Los Angeles, \$193,983. Nationally, approximately \$3.2 million was awarded for the year.

Non-HMO Comprehensive Care Developments

In addition to those developments that are strictly classified as HMO's, parallel efforts toward the provision of comprehensive health services are also being made. Although they may differ from HMO's in certain respects, particularly by being directed towards certain target elements of the population rather than the community at large, a few words about these developments are appropriate in this report.

One type of sponsorship of comprehensive care programs comes through the Office of Economic Opportunity, which has granted funding for the provision of services to specified target groups. Approximately 14 ongoing projects of this type may be found in California. One other project, formerly under the sponsorship of OEO, is currently being continued under the US Public Health Service. The OEO expects to spend approximately \$40 million nationally on pilot programs for comprehensive health care in the next two years. Several "community health networks" will be designed to serve between 100,000 and 200,000 persons, the bulk of whom will be poor.

Some funding is also being made available directly by the Health Services and Mental Health Administration (HSMHA). A contract for an experimental health services delivery system is currently in effect with the East Los Angeles Health Task Force. This funding is strictly experimental or developmental in nature and is not currently being directed to the actual provision of health care services.

Also of interest is the thrust within the Public Health Service to acquaint sponsors of potential Health Maintenance Organizations with private sources of funding, as well as with consultants to assist in planning HMO's. Although enabling legislation to guarantee loan funds used for HMO development is yet pending, government staff activities of this type nevertheless appear to be continuing on a limited basis. The expectation of enactment of this legislation is unclear at this time.

In addition, comprehensive care arrangements called Prepaid Health Plans are being effected under Medicare's Title 19. At this time, five such projects are functioning in California, including one sponsored by the San Joaquin County Foundation for Medical Care. Although a Foundation currently serves in this capacity as one such arrangement, the State Department of Health Care Services is said to view the group-practice-with-prepayment concept as more suitable for offering a comprehensive care alternative to Medi-Cal recipients. Despite the fact that the Department is encouraging organizational development so that this method of providing care under the program can become more prevalent, no funding appears to be available for start-up costs.

Some Concerns about HMO's

One of the great problems in the provision of quality care under HMO's may well be the entry on a massive basis of profit-making organizations in the health care field. Whether or not profit-making organizations are appropriate in the role of an HMO has been a source of continuing debate. Nevertheless, it is necessary that the medical profession develop guidelines for evaluating care provided and for assuring the public that they are being served in an acceptable manner. An ancillary concern relates to assurance that

each HMO is of sufficient size and fiscal soundness to remain a source of continuous care for its subscribers. Currently, the CMA Commission on Medical Services is developing criteria for evaluating HMO's. It is anticipated that these criteria will provide a basis for assuring the delivery of quality care.

At present, another important concern among physicians about HMO's is whether their development will interfere with traditional forms of private medical practice. A clear advantage, for example, is the ability of the HMO to solicit patients from private physicians. Although governmental spokesmen have repeatedly indicated that diverse modes of practice will always be able to exist, legislation enacted could, in fact, place one mode of practice in a more favorable position to other modes. This possibility has prompted the particular vigilance medical organizations have demonstrated with respect to HMO legislation.

This concern—along with the fact that the future course of HMO development in general is unclear—has created in many minds the feeling of inevitability with respect to the total preemption of the health care field under an HMO framework. Under this assumption, some physicians and groups have taken steps to develop or join with mechanisms that fulfill the requirements of an HMO. Such actions are encouraged only if the individual physician feels that participation in an HMO-type operation could be professionally satisfying and that the care provided would be of a level that he considers acceptable. Participation under other circumstances at this time would be unwarranted, since forecasts that HMO-type care will be massively available within the next few years are obviously overstated.

Among the many factors which cannot but delay the expansion of an HMO-type system of care are the following:

1. There exists a massive fiscal requirement both for the establishment of an HMO and for absorbing initial losses which may continue for three to five years. Current legislation, even if it were to be enacted, does not approach a level of funding necessary to implement stated aims.
2. The marketing of an alternative mode of health care to a sufficient number of persons to make the HMO both medically and fiscally viable

is a substantial task requiring extensive and protracted efforts. An insufficient number of subscribers during early periods of an HMO's existence imposes a fiscal burden of considerable dimension.

For all these reasons, the California Medical Association has assumed a cautious position concerning HMO's, urging that they be tested and evaluated on a pilot basis before implementation efforts are made nationally. Innovations in the organization and delivery of health care services must be shown to enhance the level of care to all segments of the population.

Points to Remember Outlined

With respect to actions or reactions of individual physicians to HMO's, the following represents a listing of several important points that should be remembered:

1. In many instances HMO's can be a creative alternative means of providing care to certain population groups or to residents of certain areas. HMO's can best be directed by physicians or with their active cooperation. If an HMO appears to be a reasonable alternative to meet a specified and identifiable need, active involvement is encouraged.

2. Despite massive governmental encouragement and potential funding available for their establishment, HMO's can only function with physician participation. Physicians must individually and cooperatively assure that professional

requirements are met and standards maintained by any such organization in which they may consider participating.

3. Physicians should remain alert to developments in their own areas. The county society can provide the best mechanism for information. The California Medical Association is also obtaining information about developments on a broader scale. Physicians should attend hospital staff meetings, especially those which may be devoted to a discussion of hospital-based HMO's.

4. Despite public relations efforts aimed at convincing the nation of a need for an all-out development in HMO-type care, it should be remembered that the American public generally remains attached to traditional health delivery methods and mechanisms. Predictions of the magnitude of HMO development have been unrealistic and cannot conceivably be met despite the degree of funding available. Physicians should interpret cautiously any such statements about the rapidity of developments in this area, either currently or in the future.

5. HMO's can provide an opportunity for profit-oriented non-professional corporations to enter the field for motives that may be less than altruistic. Physicians should be cautious in participating in programs sponsored by organizations whose orientation in health care may be subject to question. If this doubt exists about an organization, physicians should secure advice from appropriate sources such as their county medical society before undertaking binding commitments.

TALL CHILD? LOOK AT THE CHROMOSOMES

If in your pediatric practice you have children who are more than three standard deviations above the normal in height, this justifies taking a look at the chromosomes. Some, but not all of them, will have the XYY chromosome abnormality. We do know that there are no XYY's who do not have tall stature.

Not all persons with XYY abnormality have criminal tendencies. Surveys of infants and young children with this defect have been uncovered and the subjects followed rather closely for some years. About half of them, even in adolescence, have developing criminal tendencies whereas the other half appear to be perfectly normal and have no difficulties whatsoever.

—DAVID YI-YUNG HSIA, M.D., Chicago
Extracted from *Audio-Digest Pediatrics*, Vol. 17, No. 4, in the Audio-Digest Foundation's subscription series of tape-recorded programs. For subscription information: 1930 Wilshire Blvd., Suite 700, Los Angeles, Ca. 90057

Medical Economics

Physician Fee Indices in California and The U.S. Through June 1971

A Socio-Economic Report of the Bureau of Research and Planning,
California Medical Association

■ *California physicians' fees increased 2.2 percent in the first half of 1971, according to figures compiled by the Bureau of Research and Planning. Nationally, physicians' fees increased at a faster rate of 3.4 percent during the same period.*

This was the slowest semi-annual increase in the California Index since the final six months of 1968 when fees increased only 2.0 percent. A decline was also recorded in the rate of price increase for other goods and services in the first half of 1971. Nationally, the "all items" increase amounted to 2.0 percent, and the service component rose 2.1 percent.

Also included in this Report is special information on the charging patterns of physicians for office and hospital visits and data on physicians' fees in the Los Angeles and San Francisco Metropolitan Areas.

The California Physician Fee Index is a continuing survey conducted by the CMA Bureau of Research and Planning since 1962. The survey questionnaire which lists 26 medical, surgical, radiological, and laboratory procedures, elicits fee information from approximately 1,000 randomly selected physicians. Since June 1970, the procedures on the questionnaire have been listed according to the coding nomenclature used in the 1969 edition of the Relative Value Studies, published by the California Medical Association. Prior to that, the 1964 edition was used to delineate the procedure being surveyed.

CALIFORNIA PHYSICIANS' FEES increased 2.2 percent in the first half of 1971. Nationally, the U.S.

Bureau of Labor Statistics reported that physicians' fees increased at a considerably faster rate of 3.4 percent during the same period. As has been explained in previous issues of *Socio-Eco-*

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TABLE 1.—Selected Semi-Annual Figures from the U.S. Consumer Price Index and the California Physician Fee Index with Percentage Increases, December 1965-June 1971 (Dec. 1965=100)

Month and Year	United States													
	Consumer prices (all)		Services		Medical care		Physicians' fees		Dentists' fees		Hospital services		California Physicians' fees	
	Index	% Increase	Index	% Increase	Index	% Increase	Index	% Increase	Index	% Increase	Index	% Increase	Index	% Increase
Dec 1965	100.0	—	100.0	—	100.0	—	100.0	—	100.0	—	100.0	—	100.0	—
Jun 1966	101.7	1.7	102.2	2.2	102.7	2.7	103.8	3.8	101.8	1.8	104.6	4.6	103.2	3.2
Dec 1966	103.4	1.7	104.9	2.6	106.6	3.8	107.8	3.9	104.6	2.8	116.5	11.4	105.9	2.6
Jun 1967	104.5	1.1	106.8	1.8	110.1	3.3	111.4	3.3	106.8	2.1	127.3	9.3	107.9	1.9
Dec 1967	106.5	1.9	109.0	2.1	113.4	3.0	114.4	2.7	110.0	3.0	134.4	5.6	110.1	2.1
Jun 1968	109.1	2.4	112.2	2.9	116.6	2.8	117.5	2.7	112.9	2.6	142.7	6.2	112.5	2.2
Dec 1968	111.6	2.3	115.7	3.1	120.5	3.3	120.9	2.9	115.6	2.4	152.1	6.6	114.7	2.0
Jun 1969	115.1	3.1	120.1	3.8	125.3	4.0	126.0	4.2	121.4	5.0	161.2	6.0	117.4	2.4
Dec 1969	118.4	2.9	124.3	3.5	127.7	1.9 ¹	129.7	2.9	124.3	2.4	170.2	5.6	120.9	3.0
Jun 1970	122.0	3.0	130.0	4.6	132.9	4.1	135.6	4.6	127.8	2.8	180.6	6.1	126.2	4.4
Dec 1970	124.9	2.4	134.6	3.5	137.0	3.1	140.2	3.4	131.1	2.6	193.2	7.0	129.7	2.8
Jun 1971	127.4	2.0	137.4	2.1	141.8	3.5	145.0	3.4	135.6	3.4	204.2	5.6	132.5	2.2

¹ Inordinately low figure attributable to statistical adjustment rather than change in trend.

nomic Report, these two indices are not strictly comparable; nevertheless, they are both sufficiently broad measurements to be used as representing changes in fees charged by physicians. A difference in the two measures strongly suggests that variation exists in the pattern of change in physicians' fees.

The California increase was the smallest since the last half of 1968 when fees rose only 2.0 percent. Also, this recent increase is just half of that recorded for California in the first six months of 1970 (4.4 percent) and considerably less than the 2.8 percent increase during the last six months of 1970.

Nationally, the increase in physicians' fees of 3.4 percent for the first half of 1971 was exactly the same as had been reported by the BLS for the previous six-month period. This rate of increase is considerably slower, however, than the 4.6 percent increase in the first half of 1970.

Nationally, physicians' fees were recorded as having increased 8.1 percent in 1970. This was the highest 12-month increase ever reported for this index. During the same year, the medical care component of the CPI increased 7.3 percent, the highest annual rate of increase since 1947. Similarly, the California Physician Fee Index increased 7.3 percent in 1970; this was the highest increase reported since the Index was started in 1962. Index figures and semi-annual changes for

physicians' fees and other components of the Consumer Price Index are contained in Table 1.

Price Changes of Other Indices

The all items index of the CPI increased at a slower rate (2.0 percent) in the first half of 1971 than in any six-month period since the final six months of 1967. The semi-annual increases in the all items index have been steadily decelerating since the first half of 1969 when all goods and services increased 3.1 percent. Hence, the CPI increased at a slower rate in 1970 (5.5 percent) than in 1969 (6.1 percent).

The all services index, which can provide a frame of reference for evaluation of physicians' fees, increased only 2.1 percent in early 1971. This index did, however, increase at a much faster rate (8.2 percent) than physicians' fees (7.3 percent) in 1970.

The medical care component of the CPI has not followed the behavior of the all items index. As can be seen in the table, in the first six months of 1971 the medical care component increased at a faster rate of 3.5 percent than in the previous semi-annual period (3.1 percent). Furthermore, the 1970 increase in the medical care component of 7.3 percent was considerably higher than the 6.0 percent increase in 1969.

In the first six months of 1971, the rate of increase in daily hospital charges, similar to the all

items index, decelerated to 5.6 percent from a 7.0 percent increase in the second half of 1970. Throughout 1970, however, hospital charges followed the pattern of the medical care component and increased at a much faster rate (13.5 percent) than in 1969 (12.0 percent).

Dentists' fees increased at the same rate as physicians' fees (3.4 percent) in early 1971. This was a higher increase in dentists' fees than the two previous semi-annual periods (2.8 percent in the first half of 1970 and 2.6 percent in the second half of 1970).

Special Tabulations Test Physician Understanding of RVS

The Physician Fee Index survey questionnaire uses the key words "brief" and "limited" to distinguish a physician visit for a relatively simple problem requiring a short period of time from one which may include a brief or interval history, examination, discussion of findings and/or rendering of services. In terms of their "relative values" the former procedure is listed at 12.0 and the latter at 16.0 units of value when performed in an office and 20.0 units in a hospital. These distinctions are contained in the 1969 California *Relative Value Studies*.

In the course of analyzing the June 1971 Physician Fee Index, special information was prepared to evaluate physicians' understanding of these distinctions as reflected in their charging practices. Table 2 contains comparisons of usual charges indicated by physicians for brief and limited, office and hospital visits.

Billing Practices, 1969 RVS Often Differ

Of those physicians participating in the Physician Fee Index Survey, 400 listed fees for both a brief and a limited office visit. In spite of the definitions and varying unit values in the 1969 RVS, nearly one-third (32.8 percent) of these physicians indicated that they charge the same amount for a brief office visit as they do for a limited office visit. Furthermore, 5.0 percent of these 400 physicians charged more for a brief office visit than a limited visit. Similarly, of 363 physicians who listed fees for both brief and limited hospital visits, 32.5 percent charge the same for both types of visits and 7.2 percent charge more for a brief hospital visit than a limited hospital visit. These patterns suggest that not all physicians understand the nuances of difference intended between these levels of service.

TABLE 2.—Comparisons of Usual Charges Indicated By Physicians for Certain Types of Visits, California, June 1971

Comparison	Percent of Physicians Indicating:		
	Higher Charge	Same Charge	Lower Charge
Brief vs. limited visit:			
Office	5.0%	32.8%	62.2%*
Hospital	7.2	32.5	60.3*
Brief office vs. brief hospital visit	3.7	34.7*	61.6

*Represents 1969 RVS relationship

Hospital Visits More Costly than Office Visits

A comparison of the fees charged by 380 California physicians for a brief office visit and a brief hospital visit shows the majority (61.6 percent) charge more for the hospital visit than the office visit. The 1969 RVS, however, reflects a pattern of charges which valued a brief hospital visit and a brief office visit equally. This suggests that physicians' charging patterns have changed somewhat since the 1969 RVS was developed.

CMA Compiles Indices for Metropolitan Areas

The CMA Bureau of Research and Planning has in the past compiled only a statewide Physician Fee Index. In this survey period, however, index figures for the Los Angeles and San Francisco Metropolitan Areas were also developed.¹ Approximately 180 physicians in the Los Angeles area and 100 physicians in the San Francisco area provided the data for these index figures. Areawide figures may become a regular feature of this continuing survey.

The California Physician Fee Index Survey showed physicians' fees in the San Francisco Metropolitan Area increased 2.7 percent between December 1970 and June 1971; fees in the Los Angeles area increased 2.1 percent during the same period. The Bureau of Labor Statistics reported increases of 4.9 percent for the San Francisco area and 3.8 percent for the Los Angeles area.² Index figures for the two metropolitan areas and California are contained in Table 3.

¹ The Los Angeles Metropolitan Area includes Los Angeles and Orange counties. The San Francisco Metropolitan Area includes San Francisco, Contra Costa, Alameda, Marin, San Mateo, and Solano counties.

² As noted earlier, the two indices are not exactly comparable; this undoubtedly accounts for part of the variation in rates of increase reported by the BLS and the CMA. The two indices can be utilized, however, for comparing general trends. Briefly, the BLS index is based on seven procedures, including four types of physicians' visits and three surgical procedures. As mentioned above, the CMA index is based on 26 procedures. There are also variations in the number of physicians surveyed for each index.

TABLE 3.—Semi-Annual Increases in Physicians' Fees, as Reported by the U.S. Bureau of Labor Statistics and the California Medical Association

Source/ Region	1969		1970		1971
	June	December	June	December	June
US Bureau of Labor Statistics:					
Los Angeles	3.7%	5.8%	5.7%	1.3%	3.8%
San Francisco	1.3	3.4	5.3	2.7	4.9
California Medical Association:					
Los Angeles	N/A	N/A	N/A	N/A	2.1
San Francisco	N/A	N/A	N/A	N/A	2.7
California	2.4	3.0	4.4	2.8	2.2

Impact of Wage-Price Freeze

Although the total effect of the wage-price freeze is still not evident, the rapid increase in medical care costs experienced in 1970 and early 1971 should not continue throughout 1971. When the wage-price freeze ends on November 13, the President's Committee on the Health Services

Industry will play an advisory role in anti-inflationary measures within the health care industry. This combination of the wage-price freeze and the anti-inflationary measures taken by the government in Phase II of the President's economic plan should at least stabilize health care costs in the second half of 1971.

IPPB FOR ACUTE CROUP

Ten years ago anesthesiologists at Primary Children's Hospital began treating the acutely obstructed croup patient with intermittent positive pressure breathing (IPPB) and nebulized racemic epinephrine. When the literature began to report sequelae from nasotracheal intubation and lack of efficacy of steroids, we decided to review our ten-year experience using IPPB. The efficacy of this treatment has been vividly apparent to us from the beginning since the results are immediate and the improvement is dramatic. There is no difficulty recognizing whether the treatment is effective.

We have conducted a careful survey of the records of all patients seen at Primary Children's Hospital with a diagnosis of croup over the past ten years. We have excluded from this survey epiglottitis and croup of noninfectious origin. We have recognized definite benefits and a total lack of sequelae over this ten-year period. Most significant is the total absence of tracheotomies and intubations for the past seven years and a corresponding absence of mortalities. Our experience over the past ten years has been 100 percent, that is, every patient who had croup responded dramatically to the IPPB therapy when it was given properly. The incidence of tracheotomies has dropped to zero in those patients who received IPPB. A few croup patients with severe obstruction failed to respond as expected. On these occasions the consulting anesthesiologist found either that the therapist had been using faulty equipment or had not followed the protocol. A subsequent properly given treatment was always followed by marked improvement.

—JOHN C. ADAIR, M.D., Salt Lake City
Extracted from *Audio-Digest Anesthesiology*, Vol. 13, No. 10, in the Audio-Digest Foundation's subscription series of tape-recorded programs. For subscription information: 1930 Wilshire Blvd., Suite 700, Los Angeles, Ca. 90057

PUBLIC HEALTH REPORT

Frederick B. Hodges, M.D., Chief Deputy Director, State Department of Public Health

Change in Smallpox Vaccination Policy

*Report of the California Department of Public Health
ad hoc Committee on Smallpox Vaccination*

On September 30, 1971, the U.S. Public Health Service formally accepted the recommendation of its Advisory Committee on Immunization Practices to discontinue routine smallpox vaccination in this country in favor of a selective vaccination program for those population groups who may be exposed to smallpox. This recommendation was also accepted by the Infectious Disease Committee of the American Academy of Pediatrics, the California Conference of Local Health Officers, and the California State Department of Public Health.

The pertinent factors influencing the policy change for the discontinuance of routine smallpox vaccination are:

1. *The absence of smallpox from the United States for the past 22 years.*

The last documented cases of smallpox in this country occurred in 1949 secondary to an imported case from Mexico (Mexico has been smallpox-free since 1955).

2. *Successes achieved by the WHO sponsored global smallpox eradication program begun in 1967.*

In the mid-1940's, 80 countries reported smallpox and a majority of the world population lived in smallpox endemic areas. In 1966, only 43 countries, 28 of which were considered to be endemic areas, reported smallpox. At the end of 1971, after five years of systematic smallpox eradication efforts, the number of countries reporting smallpox (variola major) was reduced to seven (Afghanistan, Ethiopia, India, Indonesia, Nepal, West Pakistan and

Sudan). In the Americas, Brazil has been the only country reporting indigenously transmitted smallpox (variola minor) in recent years. Due to an intensified eradication program in that country, smallpox is well on its way to eradication there. No cases of smallpox have been reported from that country since April of 1971; however, two years of active surveillance are required after the last case has been detected before a country can be declared smallpox free.

3. *The decreasing probability of smallpox importation into the United States.*

Estimates based on the three factors governing the probability of smallpox importation into the United States — (a) the number of travelers from endemic countries entering the U.S.A.; (b) the immunity status of travelers, and (c) the incidence of smallpox in endemic countries — show that for conditions operant in 1970, the United States could expect one importation every 12 years. With the continuing success of the worldwide smallpox eradication program, this probability will soon approach zero.

4. *The risks of smallpox versus the risks of vaccination complications.*

In the United States an average of 7.5 deaths occur each year secondary to complications of smallpox vaccination (post-vaccinal encephalitis, eczema vaccinatum and vaccinia necrosum), as well as hundreds of other serious non-fatal complications. In Europe, during the past five years each imported case of smallpox has been associated with an average of ten secondary cases and 0.5 deaths. Based on this experience, it would require 15 small-

The committee is composed of: Carolyn B. Albrecht, M.D., Erwin H. Braff, M.D., Henry B. Bruyn, M.D., James Chin, M.D., Moses Grossman, M.D., Ichiro Kamei, M.D., Ronald R. Roberto, M.D., and Paul F. Wehrle, M.D.

pox importations into the United States per year to produce the same mortality currently associated with vaccination in the United States.

5. *Failure of routine infant vaccination to produce effective population ("herd") immunity.*

There is no doubt that smallpox vaccination provides excellent individual immunity to smallpox; however, solid immunity lasts for only three to five years after vaccination. After 20 years, vaccination appears to have little effect in preventing infection with variola major, although a community which at one time has been vaccinated may have some advantage over an unvaccinated community as far as death is concerned. In order to have a high population immunity, it would be necessary to have universal infant vaccination and revaccination at regular intervals throughout life. Vaccination practices in the United States have clearly failed to achieve herd immunity in recent years. Public Health Service survey data of U.S. smallpox vaccination status conducted in 1968 indicate that while 90 percent of the population has been vaccinated by age 15 years, less than 5 percent of the U.S. adult population receives vaccinations in any one year; most of them represent revaccination for international travel.

6. *Epidemiologic control of smallpox importations.*

In Europe, importations of smallpox have been effectively controlled by limited epidemiologic measures through isolation of cases, identification and surveillance of contacts and selective, limited vaccination of those at risk. The epidemiologic capability and machinery to control importations by these means exist in the United States at the federal, state and local levels. Given the present inadequate levels of community or "herd" levels of immunity to smallpox in the United States, the epidemiologic control of smallpox importations by vaccination of case contacts ("ring" vaccination) is the only logical alternative for dealing with the problem in the present era.

The Public Health Service recommendation that the long-standing traditional medical practice of universal infant vaccination now be abandoned in favor of limited, selective vaccination of individuals at risk to smallpox has led some physicians to raise several important questions

regarding this new policy. Accordingly, the State Health Department convened an *ad hoc* committee of experts from the academic and public health medical community to reply to these queries. The following questions and answers are offered for further information.

Question: What is specifically meant by the Public Health Service recommendations that "public health efforts should be devoted to assuring adequate immunization of *all* personnel involved in health services and of *all* travelers to and from continents where smallpox has not been eradicated"?

Answer: Health Personnel. The State *ad hoc* committee considers that all medical personnel who may have face-to-face contact with a potential smallpox patient should continue to receive routine smallpox vaccination as long as the risk of exposure exists. Especially important are those who work in hospitals, for 50 percent of cases associated with importations in recent European experience are acquired in hospitals. The American Hospital Association will soon distribute to all hospitals specific details regarding guidelines for vaccination of hospital employees. Emphasis must be placed on protection of patients particularly susceptible to vaccinia such as persons with eczema, chronic dermatitis, burn wounds, and altered immune states from disease or therapy. Physicians with medical practices where imported cases may be encountered should also strongly consider vaccination of their staffs. As far as public health workers are concerned, the *ad hoc* committee felt that only those employees who may come into contact with potential smallpox cases or laboratory specimens from suspected cases, such as laboratory workers, communicable disease investigators, public health nurses and physicians, need be routinely vaccinated. To maintain full immunity to smallpox, each of the above categories of persons at risk should be revaccinated at least every three years.

International Travelers. All persons traveling to regions considered endemic for smallpox should be vaccinated before their departure from the United States. It is the recommendation of the Public Health Service that persons traveling to Brazil, to any country in Africa and to any country in Southeast Asia, particularly Indonesia, Afghanistan, Nepal, India and Pakistan, be vaccinated against smallpox for their own protection. In January, 1972, the Public Health Service

announced that it neither requires nor recommends immunization against any disease for Americans traveling to Europe or the U.S.S.R. Although U.S. travelers may now go and come from Europe without vaccination certificates, it must be recognized that other smallpox-free countries in the Middle East, Africa, Asia and South America may continue to require valid smallpox vaccination certificates of travelers even if entering directly from the U.S. While international regulations do not require that revaccinations be read at seven days as with primary vaccinations, it is desirable that this be done so that if a major reaction ("take") has not been obtained, the traveler can be revaccinated.

Other. Individuals such as taxicab drivers; sea-port and air terminal workers need not be routinely vaccinated since experience has not shown them to be at special risk.

Question: Is it better to vaccinate infants at a time when we know that serious complications such as post-vaccinal encephalitis are relatively low, rather than to delay the primary vaccination until later in life when reactions may be more frequent and severe?

Answer: Data from the U.S. Public Health Service indicate that the frequency of severe complications, including post-vaccinal encephalitis is not significantly greater in young adults than in infants. These data include over one million primary vaccinations given to U.S. military recruits since World War II without a single fatality recorded. The British Army has had a similar experience. In addition, WHO anticipates that within five years smallpox will be eradicated totally from the world and at that time smallpox vaccination can be completely abandoned; therefore, present and future cohorts of infants who normally would bear the brunt of vaccination complications under a policy of routine vaccination will be spared these risks both now as infants and later as adults as vaccination will no longer be necessary for international travel.

Question: Won't abandonment of routine smallpox vaccination lead to a potential disaster when "millions" of persons will have to be vaccinated in response to an imported case of smallpox?

Answer: "Mass" smallpox vaccination is *not* the approach to the containment of smallpox after importation. Analysis of European experience in the past 20 years indicates smallpox does not spread rapidly after importation. In 1951-1960

the average importation resulted in 25.8 cases. By 1965-70 this average had declined to 10.1 cases. Clearly, there has been a decline in the probability of spread as the result of more aggressive epidemiologically-directed control measures. Also, it is unlikely that the number of cases per importation would have been this high if health personnel had been adequately protected, since almost 50 percent of infections were acquired in hospitals.

If smallpox were introduced into the United States, it is unlikely it would spread quickly enough to evade the containment measures of case detection, isolation, surveillance of contacts and *selective vaccination* of those potentially exposed.

Procedures which have been successful for the prevention of imported cases of smallpox into the United States and which will be maintained and intensified are as follows. Quarantine inspectors are stationed at all international ports to observe travelers from smallpox-infected countries. Travelers without valid vaccination certificates are placed under surveillance orders for the incubation period of smallpox. A suspected case would immediately be placed in isolation until a definite diagnosis was made. During this period the resources of local, state and federal health agencies would be alerted for prompt activation of epidemiologic activities to identify, trace, vaccinate and keep under observation all the patients' contacts pending confirmation of the diagnosis.

Question: Will smallpox vaccine become increasingly difficult to obtain for its limited use in international travelers and medical personnel, and what will happen to vaccine supplies should a national emergency arise?

Answer: The U.S. Public Health Service has assured that supplies of smallpox vaccine will be sufficient for its recommended use. In addition, a stockpile of several million doses of smallpox vaccine is being stored by the Public Health Service in the event of a national emergency.

Question: What services and facilities are available in California for diagnosis of a suspect case of smallpox?

Answer: The early diagnosis of smallpox is the key to effective containment of imported smallpox. The State Health Department and its smallpox consultants* stand ready to respond to all

*Smallpox consultants: *Northern California*—Moses Grossman, M.D., San Francisco General Hospital; *Southern California*—Paul F. Wehrle, M.D., Los Angeles County General Hospital.

requests for diagnostic consultation when smallpox is considered. The diagnosis should be considered in all individuals manifesting compatible signs and symptoms who have traveled in a smallpox-infected area within the previous two weeks regardless of their vaccination history. All suspect cases should be reported immediately by telephone to the health department. Rapid diagnostic procedures such as electron microscopy and immunofluorescence techniques are available at the State Viral and Rickettsial Disease Laboratory to aid the physician in evaluation of suspect cases.

Question: Have provisions been made for ongoing evaluation of this change in vaccination recommendations?

Answer: The State Department of Public Health and other groups have requested the United States Public Health Service to review this policy change and the status of global smallpox eradication annually.

Conclusion

Smallpox vaccination from the time Jenner introduced the procedure in 1798 has been an invaluable tool in preventive medicine. Discon-

tinuation of routine vaccination in smallpox-free nations as has occurred in New Zealand and recently in England and the United States attests its success. Active support of the who global smallpox eradication program will lead eventually to the first infectious disease eliminated from the planet earth by the directed efforts of man. Although progress is being made on this front, it must be strongly emphasized that immunizations which are routinely given in this country for other endemic infectious diseases cannot be de-emphasized (diphtheria, pertussis, tetanus, rubeola, rubella, and poliomyelitis) as these diseases continue to pose an individual and public health threat if efforts to eliminate them through immunization are allowed to slacken.

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SOAP DISPENSERS AS CULTURE MEDIA

I believe the days of the standard scrub brush and the foot-operated dispenser of liquid soap are over. I would hope so, in any event. We have found that such soap dispensers are literal culture media. The individually wrapped, soap-impregnated scrub brush is so much safer and avoids the possibility of contamination of the dispenser. Next one would hope that we would go rapidly to a no-faucet sink, one of which is available now on the market. Nothing has to be pushed by hands, feet, elbows or other parts of the body to start the water running. It works by way of a proximity button so that there is no means of contamination and no standing column of water to become contaminated. (I refer here to the sinks that are foot operated or knee operated in which a standing column of water sends out a stream of bacteria for the first several minutes of the water flow.)

—HAROLD LAUFMAN, M.D., New York City
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Information

Chronic Occlusive Arterial Disease of the Limbs

JESS R. YOUNG, M.D.

Material Supplied by the American Heart Association

CHRONIC OCCLUSIVE ARTERIAL DISEASE of the limbs may cause no symptoms in mild cases, intermittent claudication in moderate cases, and gangrene and amputation in severe cases. Most patients with occlusive disease are men, beyond the age of 45 years, and they have symptoms in the legs rather than in the arms. With the aging of our population, the number of patients with this problem will increase. Proper management requires an accurate diagnosis of the basic disorder, an evaluation of the extent and the rate of development of the occlusive process, and an assessment of the patient's general status.

Etiology

The major cause of occlusive arterial disease is atherosclerosis obliterans (ASO), which accounts for more than 95 percent of occlusions of the extremities. Less common causes included thromboangiitis obliterans (Buerger's disease), other forms of arteritis, chronic ischemia resulting from embolic arterial occlusion in a limb that survives the acute episode, arterial trauma, thrombosis of aneurysms, and dissecting aneurysms.

Symptoms

The most common and earliest symptom of patients with occlusive arterial disease is inter-

mittent claudication. This is a discomfort that occurs only when the patient is walking, and disappears within one or two minutes after he stops walking. The discomfort is variably described as a cramping, a pain, an ache, a sense of fatigue, a tiredness, or a heaviness. The patient need not sit down to obtain relief, and at no time is the discomfort experienced when the patient is lying, sitting, or standing. The location of the symptoms is dependent on the location of the occlusion, and the discomfort can occur in the foot, calf, thigh, buttock, or arm.

Pain at rest indicates a more severe degree of ischemia. It is generally worse at night and may be temporarily relieved by dependency of the limb or by walking. The patient may find that he can sleep only by sitting in a chair with his legs down. The pain of ischemic ulceration and gangrene is more severe, usually not relieved by dependency, and is difficult to control even with narcotics.

Diagnosis

To determine the presence and severity of arterial insufficiency, no unusual or elaborate equipment is necessary. An adequate evaluation may be accomplished in any physician's office.

The most important finding on physical examination is an absence or a decrease in amplitude of arterial pulsations. A good index as to the severity of ischemia is the change in color of the feet with alterations in positions of the limb. After elevating the leg for about one minute, an abnormal pallor in the foot and leg will appear when there is significant ischemia. On subsequent dependency, there is a delay in filling of the veins beyond the normal 10 to 15 second period. When the color returns, it may be bright red, the so-called "rubor on dependency." As arterial insufficiency worsens, ischemic ulcers may develop on the toes and dorsum of the foot.

Arteriography is not necessary unless arterial surgery is contemplated.

Treatment

Medical Treatment

All patients are asked to refrain from smoking. Smoking will cause peripheral vasoconstriction in almost all persons and is quite likely an important etiologic factor in arteriosclerosis. The patient with thromboangiitis obliterans must

From the Department of Peripheral Vascular Disease, The Cleveland Clinic Foundation, Cleveland.

strictly avoid all forms of tobacco, for hypersensitivity to nicotine is believed to be the cause of this disease.

Postural exercises are time consuming and have proved ineffective. However, walking is of great benefit in developing collateral circulation, and the patient is asked to walk as far and as often as possible. Continued walking past the point of intermittent claudication eventually will bring about greater increase in collateral flow than stopping at the first sign of claudication.

The patient with severe ischemia is advised to elevate the head of the bed (4 to 6 inches) to increase the blood flow to the feet. Great care must be taken to prevent further damage to the severely ischemic limb. The heel should be protected with either a layer of sheep skin or a padded boot. Pressure from bed clothes should be prevented by the use of a foot cradle.

Repeated use of analgesics may be necessary for temporary relief of ischemic pain. A tranquilizer may be helpful in alleviating the anxiety often associated with severe pain and may potentiate the effect of the analgesics. Narcotics should be used with caution because the chronicity of ischemic pain may lead to addiction.

The precipitating cause of many severely ischemic lesions is trauma from mechanical, chemical, or thermal sources. Each patient should therefore be given detailed instructions concerning the care of his extremities and the avoidance of trauma. He should be carefully advised regarding care of his nails, avoidance of hot and cold temperatures, and proper treatment of athlete's foot.

The value of oral vasodilator drugs is a controversial subject. Most authorities have not found them to be effective, but if some attempt at oral vasodilatation is desired, an ounce of whiskey or brandy or a glass of wine, three or four times daily, may be recommended.

An attempt should be made to control other associated disease. Phlebotomy may help to decrease the occurrence of thrombotic episodes in polycythemia vera. Reduction of hyperlipidemia and control of hypertension may have some effect in retarding progression of arteriosclerosis. Diabetes should be kept under good control,

not only to retard arteriosclerosis, but also to help prevent complications such as infection and neuropathy which make the management of arteriosclerosis more difficult.

Surgical Treatment

In selected patients, arterial surgical reconstruction may have much to offer. In some patients with long periods of continuing patency of vessels after surgery, especially in those patients who are operated on for aortoiliac disease, the value of surgical treatment may be great. In other patients, especially those operated upon for femoropopliteal disease, secondary thrombosis will occur in a significant number within one or two years postoperatively, and may make this procedure of little value. In addition, many patients, either because of the diffuseness of their occlusive disease or because of severe associated disease are not suitable for treatment by surgery. The decision for operation should be made only after careful deliberation. Patients who could justifiably be considered to undergo surgical procedures would include those in whom intermittent claudication is severe enough to prevent them from working in a necessary occupation, those whose claudication has been steadily worsening, and those who are already suffering from rest pain, ulceration, or gangrene.

Sympathectomy can be of great value in certain patients. This procedure will dilate only the vessels of the skin and will not improve intermittent claudication. However, minor ischemic ulcerations or superficial gangrene may be healed with this procedure, and rest pain can be eased in those patients in whom arterial surgery is not possible.

Conclusions

The prognosis for patients with chronic occlusive arterial disease is probably better than is commonly believed. With proper evaluation, intelligent management, and cooperation from the patient, the loss of limbs and lives may be reduced to a minimum. Conservative treatment remains the keystone of therapy whether or not surgery is used.

In Memoriam

Persons wishing to do so may make contributions to the Physicians' Benevolence Fund to honor the memory of a member who has died. Members of the family will be notified that such a contribution has been made and the name of the donor will be supplied.

Checks should be addressed to Physicians' Benevolence Fund, Inc., California Medical Association, 693 Sutter Street, San Francisco, Ca. 94102.

BUCKLEY, THOMAS IGNATIUS, Oakland. Died January 25, 1972 in Concord of cardiac arrest, aged 71. Graduate of the University of California Medical School, Berkeley-San Francisco, 1929. Licensed in California in 1929. Doctor Buckley was a retired member of the Alameda-Contra Costa Medical Association and the California Medical Association, and an associate member of the American Medical Association.

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BULLEY, EDWARD WILLIAM, Apple Valley. Died December 29, 1971 of heart disease, aged 64. Graduate of Harvard Medical School, Boston, 1932. Licensed in California in 1934. Doctor Bulley was a member of the San Bernardino County Medical Society.

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EWER, EDWARD GOLDSMITH, Oakland. Died December 31, 1971 of virus pneumonia, aged 65. Graduate of the University of California Medical School, Berkeley-San Francisco, 1932. Licensed in California in 1932. Doctor Ewer was a member of the Alameda-Contra Costa Medical Association.

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McKELL, DAVID McCANDLESS, JR., San Jose. Died January 14, 1972 in San Jose, aged 62. Graduate of Harvard Medical School, Boston, 1938. Licensed in California in 1948. Doctor McKell was an associate member of the Santa Clara County Medical Society.

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NEWMAN, WILLARD HODGES, San Diego. Died January 20, 1972 in San Diego, aged 82. Graduate of the University of California Medical School, Berkeley-San Francisco, 1922. Licensed in California in 1922. Doctor Newman was a retired member of the San Diego County Medical Society and the California Medical Association, and an associate member of the American Medical Association.

OTTINGER, MILLARD R., San Francisco. Died January 7, 1972 in San Rafael, aged 78. Graduate of College of Physicians and Surgeons of San Francisco, 1918. Licensed in California in 1918. Doctor Ottinger was a retired member of the San Francisco Medical Society and the California Medical Association, and an associate member of the American Medical Association.

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SMITH, JOSEPH KENT, Bakersfield. Died January 15, 1972 in Bakersfield, aged 83. Graduate of the College of Physicians and Surgeons, Medical Department, University of Southern California, Los Angeles, 1916. Licensed in California in 1916. Doctor Smith was a member of the Kern County Medical Society.

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UNSELL, IRA MAXWELL, Long Beach. Died January 5, 1972 in Long Beach of ventricular fibrillation, myocardial infarction, aged 60. Graduate of the College of Medical Evangelists, Loma Linda-Los Angeles, 1939. Licensed in California in 1940. Doctor Unsell was a member of the Los Angeles County Medical Association.

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VAN ZANDT, ALBERT VERNON, Oceanside. Died October 13, 1971 of reticulum cell sarcoma with metastases, aged 74. Graduate of Stanford University School of Medicine, Palo Alto-San Francisco, 1932. Licensed in California in 1932. Doctor Van Zandt was a retired member of the Tulare County Medical Society and the California Medical Association, and an associate member of the American Medical Association.

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WALDECK, HENRY, Los Angeles. Died January 10, 1972 in Los Angeles of heart disease, aged 78. Graduate of Julius - Maximilians - Universität Medizinische Fakultät, Würzburg, 1920. Licensed in California in 1942. Doctor Waldeck was a member of the Los Angeles County Medical Association.

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WILLIAMS, DELBERT BRADLEY, San Bernardino. Died December 28, 1971 in Corona del Mar, aged 69. Graduate of Rush Medical College, Chicago, 1928. Licensed in California in 1928. Doctor Williams was a retired member of the San Bernardino County Medical Society and the California Medical Association, and an associate member of the American Medical Association.

BOOK REVIEWS

CALIFORNIA MEDICINE does not review all books sent to it by the publishers. A list of new books received is carried in the Advertising Section.

ANESTHESIA FOR THE AGED—Paul H. Lorhan, M.D., Professor of Anesthesiology, University of California Medical Center, Los Angeles, Chief of the Department of Anesthesiology, Harbor General Hospital, Torrance; with a Foreword by William P. Longmire, Jr., M.D., Professor and Chairman, Department of Surgery, UCLA School of Medicine, Los Angeles. Charles C Thomas, Publisher, 301-327 East Lawrence Avenue, Springfield, Ill. (62703), 1971. 153 pages, \$8.25.

Anesthesia For the Aged presents a discussion of the physiologic changes in the aging patient. The first portion of the book, "Physiologic Considerations," contains the important factors which one may derive from the book. The references are fairly good. However, the remainder of the book is a poorly organized, repetitious discussion, deficient in some areas, and highly opinionated in others. This book does not provide a clear, logical, helpful analysis of geriatric anesthesia.

FRIEDA L. GRELL, M.D.

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PRINCIPLES OF CARDIAC ARRHYTHMIAS—Edward K. Chung, M.D., F.A.C.P., F.A.C.C., Professor of Medicine and Director, Electrocardiographic and Vectorcardiographic Laboratory, West Virginia University, School of Medicine, Morgantown. The Williams & Wilkins Company, 428 E. Preston St., Baltimore (21202), 1971. 540 pages, \$24.75.

This text is a comprehensive attempt to discuss abnormal impulsal formation and conduction from an electrophysiological and clinical point of view. Therapy is not discussed in any great detail, but the principles of treatment are woven into the clinical discussion. The author systematically reviews the anatomy, electrophysiology, hemodynamics of the heart and then reviews each type of abnormality of rhythm in sequence. The book is copiously illustrated with good legends and 505 illustrations; not only do they add considerably to the text, they reveal the wide experience of the author.

In addition to the more formal, routine discussions, there is a good chapter of Wolff-Parkinson-White Syndrome and one on parasystole. Each chapter is followed by a comprehensive bibliography for further review by the reader.

One can always spot areas of disagreement with the presentation and interpretation of some of the complex arrhythmias, but in general the presentation of the subject is sound and conforms to the majority of authoritative opinion. His diagnostic criteria for various types of arrhythmias could be improved and errors are probably produced because of his attempt to make a short, concise statement. For example, his definition of a ventricular, premature contraction is "when a wide, bizarre QRS complex appears prematurely without a preceding ectopic P wave." This is an inadequate statement; such an arrhythmia could very well be supraventricular and junctional in origin, with aberrant conduction. Similarly his discussion of hemodynamics is often too brief and general and too few details are given. The phrase "significant hemodynamic abnormalities" is used without definition and a good example is in the discussion of atrial ventricular nodal arrhythmias when he states: "Paroxysmal A-V

nodal tachycardia seldom produces a significant hemodynamic abnormality in spite of the rapid rate. Conversely, non-paroxysmal A-V nodal tachycardia almost always produces serious hemodynamic alterations in spite of a relatively slow rate." Many readers will disagree with the author's statement that the most common cause of cardiac arrhythmias is coronary artery disease. One might wonder about digitalis, functional abnormalities, rheumatic heart disease, etc. His statement also that atrial fibrillation is a well known manifestation of coronary heart disease could be disputed; actually it is quite uncommon in patients with unequivocal angina pectoris. One would also question his statement that the PR interval or the A-V conduction time is the time involved for the impulse to reach the A-v node, when it actually is to reach the point of division of the His bundle.

One area in which the author does not use modern terminology concerns nodal rhythm. In spite of a good deal of evidence that the A-v node is not the site of impulse formation, but only of impulse conduction, the author in many places talks about the A-v node producing an impulse. In conformity of modern usage, the author should in the next edition change his terminology to *junctional supraventricular rhythms, bundle of His rhythms*, etc., rather than *nodal rhythms* and *nodal arrhythmias*.

One is disappointed to find practically no discussion of His bundle recordings and their use in cardiac arrhythmias in the light of recent work showing the theoretical and practical advantages of His bundle recordings. One would have expected a rather full treatment of the subject.

In spite of the above mentioned shortcomings, the book is a very useful addition to the cardiac literature. It is clearly written, well illustrated and can be recommended to students and general physicians.

MAURICE SOKOLOW, M.D.

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HANDBOOK OF PEDIATRICS—Ninth Edition—Henry K. Silver, M.D., Professor of Pediatrics, University of Colorado School of Medicine; C. Henry Kempe, M.D., Professor of Pediatrics and Chairman of the Department, University of Colorado School of Medicine, Denver; and Henry B. Bruyn, M.D., Clinical Professor of Pediatrics and Medicine, University of California, San Francisco, School of Medicine. Lange Medical Publications, Drawer L, Los Altos, Ca. (94022), 1971. 713 pages, \$6.50.

The survival of any text or handbook to the ninth edition is ample testimony to its usefulness as a source of ready information for students, pediatric house officers and those physicians responsible for the care of children. This most recent edition contains an immense amount of information on normal values, various diagnostic procedures useful in identifying the etiology of specific problems, the methodology of tests and the expected results. In addition, much of the data is available for quick and easy reference as it is supplied in tabular form.

Virtually all of the commonly encountered problems that befall children are described briefly and a logical method of verifying the diagnosis and managing the patient during the illness or behavioral disturbance is pro-

vided. While one may argue with some features of the therapy suggested, seldom do two physicians agree entirely as to the specifics.

In the opinion of this reviewer, this book should be available on every pediatric service and in every office of those concerned with the care of children. It does not, as the authors candidly indicate, replace the more detailed and extensive standard treatises on the diseases of children, but its usefulness lies in the ready access to the essentials of the problems at hand. The authors are to be commended for this volume, and we may hope for timely editions in the future.

PAUL F. WEHRLE, M.D.

* * *

MUSCLES—Testing and Function—Second Edition—Henry Otis Kendall, P.T., Formerly Director, Physical Therapy Department, Children's Hospital School, Baltimore; Florence Peterson Kendall, B.S., P.T., Faculty member, Department of Physical Therapy, University of Maryland School of Medicine; and Gladys Elizabeth Wadsworth, Ph.D., P.T., Associate Professor, Department of Anatomy, University of Maryland School of Medicine. The Williams and Wilkins Company, 428 East Preston Street, Baltimore, Md. (21202), 1971. 284 pages, fully illustrated, \$19.75.

The authors, having had a vast experience in muscle testing and grading, especially with poliomyelitis patients (fortunately quite uncommon now), have continued their studies and present an atlas of definite value in an understanding and interpretation of muscle function, normal or abnormal, and testing therefor.

Those with a special interest in musculoskeletal function and testing for such, as orthopedists, neurosurgeons, physiatrists, physical therapists, trainers and residents, will find a good presentation in this work, and it is recommended not only for reading but to have as a reference.

Excellent diagrams in color of muscles, with origin and insertion, also nerve supply, are shown and offer a fine opportunity for quick anatomical review.

Function of normal muscles, singly and in groups, and tests for these as well as abnormal muscle function either from partial paralysis or contracture, is very well described also illustrated in pertinent photographs.

Grading of muscle strength is well discussed, including factors of gravity, also pressure, weakness, shortness, contracture, substitution and fixation, and which factors are generally not always well understood or considered in grading. Also the term "normal" is discussed, pointing out that it does differ for certain muscle function in different age groups. Movement of joints is described, some of which is known in general, but not in detail as presented.

Charts are shown depicting sensory nerve supply which can be helpful in determining neurological deficits.

Thus in review, this book is definitely recommended for those in medicine and allied activities, who have a special interest in muscular and musculo-skeletal problems, including testing for normal as well as for abnormal function.

PAUL E. McMASTER, M.D.

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CARDIOVASCULAR BETA ADRENERGIC RESPONSES—UCLA FORUM IN MEDICAL SCIENCES—Number Thirteen—Proceedings of a Conference held February, 1968. Sponsored by the UCLA School of Medicine and the University of California Extension, Los Angeles; Partially supported by a grant from Ayerst Laboratories—Edited by Albert A. Katus, Gordon Ross and Victor E. Hall, University of California Press, 2223 Fulton Street, Berkeley, Ca. (94720), 1970. 284 pages, \$20.00.

Among the most important recent advances in improved understanding of performance of the sympathetic nervous

system has been development of the concept of two different functional types of adrenergic effector sites in organs throughout the body. In the cardiovascular system, beta adrenergic receptors are located in the myocardium, while both alpha and beta receptors are present in the peripheral vascular beds. Enormous progress has been achieved in the characterization and function of these receptors which has proven to be considerably useful to the clinician, as well as to physiologists and pharmacologists. This new information is carefully synthesized in the present monograph containing the proceedings of the authoritative UCLA Forum in Medical Sciences held in February of 1968. The highlights of the symposium include presentations from 20 nationally known participants on the basic mechanisms and clinical significance of beta adrenergic stimulation and inhibition in the cardiovascular system. Emphasis is focused on the benefits and hazards which attend beta blockade with propranolol in the treatment of cardiac tachyarrhythmias, angina pectoris due to coronary artery disease, obstruction to left ventricular outflow in idiopathic hypertrophic subaortic stenosis, and hypertensive diseases. While the biochemical and structural nature of the beta receptor and related sub-receptors remains to be clarified, this book provides a concise review of the present knowledge of the pharmacology which is essential for physicians in the salutary use of beta adrenergic agonists and antagonists.

DEAN T. MASON, M.D.

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TRANSPLANTATION TODAY—Proceedings of the Third International Congress of the Transplantation Society, September 7-11, 1970, The Hague, The Netherlands—Editors: Hans Balner, Rijswijk, The Netherlands; D. W. van Bekkum, Rijswijk, The Netherlands; Felix T. Rapaport, New York City. Grune & Stratton, Inc., 757 Third Avenue, New York City (10017), 1971. 978 pages, \$25.00.

This book contains the Proceedings of the Third International Congress of the Transplantation Society held in The Hague, September 7-11, 1970. It is guest edited by Drs. Hans Balner and D. W. van Bekkum. It is really a compilation of all of the recent advances in transplantation in all of its aspects—from the most fundamental to the most recent clinical advances. In its 978 pages there is much information for the student of transplantation biology, the basic immunologist as well as clinical transplanters.

The first section of the text is devoted to general surveys of important issues in transplantation, for example the genetics of transplantation is reviewed; immunocompetent cells in graft rejection; antigen induced immunosuppression as well as immunosuppression by chemical agents; antilymphocyte serum and its mode of action; the phenomenon of immunological tolerance and enhancement as well as heterotransplantation and bone marrow transplantation. This aspect of the text should be of interest to a wide sector of the medical profession.

The text also deals with *in vitro* testing and its relationship to HL-A antigens—data is available on the mixed leukocyte culture and the role of cytotoxic antibodies in organ graft rejection. The importance of enhancing antibodies in tumor transplantation as well as organ transplant rejection is a new and interesting finding reported in this text.

For the individuals interested in clinical transplantation there is a section devoted to clinical relevance such as the relevance of HL-A phenotyping in organ transplantation and the ways in which histocompatibility grading can be carried out. The relevance of these aspects of transplantation to other species—the DLA system in dogs—and the relevance of histocompatibility antigens in other species is also included. The chemistry of trans-

plantation antigens, which will be of great interest to the specialist in the field of organ transplantation, is elaborated upon.

Finally, discussions of many of the problems in clinical transplantation, for example the transplantation of patients with Australian antigenemia, the results of cadaver transplantation for various organs including heart, liver, lung and pancreas, and the value of various types of immunosuppressive techniques—antilymphocyte serum, chemical immunosuppression as well as extracorporeal irradiation—are included. The latter part of the book is really devoted to the future of transplantation, new techniques of microsurgery and its relevance to elucidating some of the unsolved problems in transplantation as well as the role of organ preservation. The remarkable success of perfused kidneys for more than 50 hours is reported and the techniques by which this can be done on a regional basis was outlined.

Many small papers have been grouped in this book, but they are organized in a fashion whereby students with varying interests can study a section and obtain a good grasp of the part of in which they are particularly interested. The text is highly recommended because it gives the most recent status of transplantation today and what problems remain to be solved before transplantation achieves a major role in the area of clinical therapy.

The Third International Congress of the Transplantation Society was dedicated to Sir Peter Medawar, who has made many fundamental contributions to transplantation. His contributions are highlighted by Professors Brent and Woodruff.

I highly recommend this text.

SAMUEL L. KOUNTZ, M.D.

* * *

OUTLINE OF ORTHOPAEDICS—Seventh Edition—John Crawford Adams, M.D., F.R.C.S., Consultant Orthopaedic Surgeon, St. Mary's Hospital, London; Civil Consultant in Orthopaedic Surgery, Royal Air Force; Deputy Editor, *Journal of Bone and Joint Surgery*. The Williams & Wilkins Company, 428 E. Preston, Baltimore, Md. (21202), 1971. 476 pages, \$11.75.

John Crawford Adams' *Outline of Orthopaedics*, originally published in 1956, has now reached its 7th edition. The outline continues its primary objective and is intended primarily to help students. The author's endeavor to present an easily read account of our present knowledge about orthopedic surgery has been satisfactorily accomplished.

The topics of rheumatoid arthritis, gout, spina bifida and the treatment of degenerative arthritis of the hips and knee have been revised. A number of minor revisions have been made in various other chapters, however, many chapters and most illustrations have been taken over unchanged from the previous edition. The chapters on hip region, trunk and spine merit special praise. The medical illustrations are good and the improved bibliography is very adequate. Throughout the text, the author has comments following the original format, which are very welcomed when several choices of therapy are available for the care of a complex problem.

The text has followed the same original format and continues to be easily read. Because of the broad coverage, it is ideal for students in medicine, occupational therapy, physical therapy and nursing. Interns and residents of orthopedic surgery could readily use this as a basic text. The practicing physician without training in orthopedic surgery would do well to refer to this text for a rapid source of information in reference to his patients' musculo-skeletal problems.

RICHARD A. SILVER, M.D.

ABORTION—Changing Views and Practice—R. Bruce Sloane, M.D., Editor. (This book is reprinted in large part from the August 1970 issue (Vol. 2, No. 3) of *Seminars in Psychiatry*). Grune & Stratton, Inc., 757 Third Ave., New York City (10017), 1971. 182 pages, \$5.75.

This book is actually, as stated by the publisher, a reprint of the August, 1970 issue of *Seminars in Psychiatry*, with updated comments on recent experiences with the New York State liberal abortion laws. This latter is unfortunately out of date by the time of presentation because of the tremendous volume of abortions in New York in the past year.

Much of the discussion is a rehash of old material. It is interesting but I found Dr. Callaghan's 1970 book, *Abortion, Law, Choice, and Morality* a far more comprehensive and valuable work.

There are some errors, and many opinions. The time is ripe for a really comprehensive review of the New York and California statistics. As an example, the statistics from Colorado discuss a few hundred cases, less than the number performed in San Francisco alone every month.

Changing views in practice and abortion are going to change very rapidly from day to day. Legal decisions expected soon from the California Supreme Court, and others, will change this even further. Your reviewer looks forward to a similar book to this, written in 1975, which will make much of the discussion presented here academic.

GEORGE K. HERZOG, JR., M.D.

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A TEXTBOOK FOR MEDICAL ASSISTANTS—Second Edition—M. Murray Lawton, M.D., Administrator of the Berkeley School; Director, In-Service Training, Berkeley East Hospital, Santa Monica; and Donald F. Foy, B.S., M.S., M.P.H., Director, Department of Health Manpower, American Medical Association, Chicago, Illinois. The C. V. Mosby Company, 3207 Washington Blvd., St. Louis, Mo. (63103), 1971. 473 pages with 137 illustrations, \$9.85.

If the authors were starting to write this book today and wanted a maximum readership they might give it the title "Everything the Modern Medical Assistant Wants to Know, but Doesn't." They take up in detail, in successive chapters, all the knowledge and all the problems which they feel the medical assistant should have. Their objective is to provide a basic reference text for all those actively engaged in careers of "medical assisting" as well as for students in the field. (There is a certain elementary quality which reflects their desire to make it useful to students taking their initial training as medical assistants.) There is a glossary with each chapter, particularly useful to the student or to the assistant learning on the job.

The book is divided into two parts: Business Practices, and Clinical Practices. Business Practices takes up a wide variety of subjects including public relations, social and professional amenities, medical ethics and jurisprudence, processing mail, patients' records, private health insurance, the role of government in health, medical office bookkeeping, medical office economics, banking activities, payroll deductions and medical office housekeeping. This portion of the book is both detailed and comprehensive. It can be recommended highly to both students and those in the active business of assisting physicians.

The second part of the book on Clinical Practices is likewise extensive although there is some difficulty in covering the field as well as in the first part. It may be subject to criticism by physicians whose opinions vary from those who have been the authorities for the authors. The chapter titles include anatomy and physiology, common medical terminology, preparation of patients, medical and surgical office procedures, drugs and solutions, sterilization pro-

cedures for the medical office, hypodermic injection technique, technique of simple laboratory operations, routine urinalysis, hematology, medical office bacteriology, electrocardiography, medical office x-ray procedure, emergencies in the medical office.

It may be worth noting that, although this book has just been published in the year 1971, some of the details listed already require up-dating. For example: In chapter 18, page 277, on payroll deductions, the authors state that if the income tax withheld from employee wages plus the combined employee and employer F.I.C.A. taxes for a given month amount to more than \$100, the total must be deposited by the employer on or before the fifteenth day of the following month in a Federal Reserve Bank. On the other hand, specific instructions in the current form 941, the amount is \$200.00.

On the whole, this book can be recommended as a succinct volume to be either a text for the student or a reference for the medical assistant. Incidentally, it can be of service to the physician to keep in his office for his own information as well as that of his assistant.

EDGAR WAYBURN, M.D.

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DIAGNOSTIC APPROACHES TO PRESENTING SYNDROMES—Jeremiah A. Barondess, M.D., Editor, Clinical Professor of Medicine, Cornell University Medical College; Attending Physician, The New York Hospital, New York. The Williams & Wilkins Company, 428 E. Preston, Baltimore, Md. (21202), 1971. 547 pages, \$21.50.

In an age in which technological advances may bewilder the physician caring for sick patients, this bedside approach to diagnosis is genuinely refreshing. Thirteen problem areas of internal medicine have been selected from the various specialty areas; for example: mitral and aortic regurgitation, fever of unknown origin, weakness, unresolving pneumonia, demineralization of bone. The clinical presentation and pathologic physiology are reviewed in detail, and a differential diagnosis is thoroughly analyzed with a special eye to clinical points suggesting specific diagnoses. Often a logical stepwise approach to diagnosis is outlined and the merit of common diagnostic techniques is weighed. The contributing authors approach their topics with varying format—some are more analytical, others more anecdotal; but all chapters seem authoritative and the bibliographies are generally extensive and current. The lead chapter on mitral regurgitation is particularly outstanding.

The House Officer, generalist, or internist who enjoys approaching diagnosis from presenting syndromes rather than from specific disease entities will find this book helpful and often truly stimulating.

W. MORRIS H. NOBLE, M.D.

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TEXTBOOK OF MEDICAL PHYSIOLOGY—Fourth Edition—Arthur C. Guyton, M.D., Professor and Chairman of the Department of Physiology and Biophysics, University of Mississippi School of Medicine. W. B. Saunders Company, West Washington Square, Philadelphia, Pa. (19105), 1971. 1032 pages, \$18.50.

This book exemplifies some of the dilemmas inherent in present-day textbook writing. First, should multiple authors write on their specialties in a diversity of writing styles and without much correlation between chapters, or should one good teacher present a consistent viewpoint and writing style throughout the book? Here a single author does not prevent duplication of ideas and phrases in different parts of the book, where, for example, the principles of diffusion are presented twice, where the same general ideas of lateral inhibition are re-presented (each time in-

adequately) in the contexts of the visual, auditory, and somatosensory systems, and even where the ideas that 120 meters is longer than a football field (when mentioning axon conduction velocity) appears more than once. The style of the book is consistent, with an effort to always give examples of generalizations and to offer many figures. Unfortunately, the examples are often more difficult to understand than are the principles (as in the case of illustrating the idea of mathematic integration by the example of integrating the first derivative of a function to obtain that function), while the figures quite frequently raise more questions than they answer (by having unexplained symbols, fictitious results, confusing arrows, and other simplifications, apparently for didactic purposes)—all of which frustrate the careful reader. The whole approach seems to indicate a codification in written form of material found successful in small-group blackboard teaching; if so, the material suffers in the transfer.

A second dilemma relates to whether the material should be presented "in depth" or in a more superficial manner. This book strongly opts for the second, which in turn gives it a dogmatic mien. Although there are references at the end of each chapter, none are cited in the text, and the only names of famous investigators that creep in do so as eponyms. Small attempts are made to communicate the present status of knowledge, but these are too often inaccurate, as when excitation of postsynaptic neurons is "believed" to be due to an excitatory transmitter, soon followed by the dogmatic statement that "synaptic vesicles contain the excitatory transmitter." The overall approach leads to statements which are not harmful in context, for a superficial reader, but which will make it difficult for a motivated student to go to any other source without becoming confused: (1) The diagrams for servo-control loops are unorthodox without special benefit and with room for considerable confusion in terminology. (2) A fundamental equation of axonal conduction (the Goldman) is called by the name of a similar, but crucially different equation (the Nernst). (3) The statements of the Bell-Magendie law and of the Frank-Starling law both confuse the consequences of a law with the principle itself. (4) The infamous "all-or-none" law of axonal conduction is completely misrepresented. (5) It is implied that a monophasic action potential cannot be obtained by means of extracellular electrodes (most medical students successfully record such potentials in laboratory exercises). (6) The mechanism of action of excitatory transmitter on the postsynaptic membrane is ascribed to permeability changes at one place, to Na^+ alone, at another, to both Na^+ and K^+ , and at a third, to "essentially all ions."

The final and major dilemma of modern "large" textbooks of physiology is: who will read it? With the rapid decline in basic science teaching in medical education, the role of the thorough, all-inclusive, authoritative reference book is called into question. Possibly graduate students and a few medical students may want to delve into the subject more deeply than the average present-day professional student, but this book, as already indicated, is not suited for such students (and probably was not so intended). On the other hand this 1000-page textbook is probably too long (despite its efforts to be "simple") for present day cut-down quick-survey medical-physiology courses. This problem is not the fault of the author, but of our "curricular convulsions" (that is non-purposive, massive, uncoordinated movements of subject matter). How authors will find their new readerships is not clear, but it is of interest that the same author offers this material in two other versions, one 30 percent and the other 50 percent shorter.

DON L. JEWETT, M.D.



Isoniazid Chemoprophylaxis of Tuberculosis

DANIEL JENKINS, M.D., *Oklahoma City*, AND
FRANK F. DAVIDSON, M.D., *Boston*

■ *A major step toward the eradication of tuberculosis in the United States has been the use of isoniazid for chemoprophylaxis in certain persons who have positive tuberculin skin tests but no other evidence of active infection. Chemical trials have demonstrated the effectiveness of chemoprophylaxis in groups where there is a relatively high risk of active tuberculosis. However, only the practicing physician can identify and offer chemoprophylaxis to many other susceptible persons. Even if the patient is a candidate for isoniazid, the risk of developing tuberculosis must be weighed against the cost and possible adverse effects of the drug. If isoniazid is given, the physician must be alert to the signs of possible drug toxicity. If isoniazid is not given, he must anticipate the development of active tuberculosis in susceptible persons.*

CHEMOPROPHYLAXIS IN TUBERCULOSIS generally refers to the use of Isoniazid (INH) to prevent tuberculous infection or its manifestations. Primary prophylaxis refers to giving INH to persons not yet infected with tuberculosis or to those who are presumably infected but who have not yet developed delayed hypersensitivity. Secondary prophylaxis refers to giving INH to persons with positive tuberculin skin tests who do not have clinically active disease. This is the chief concern of this paper. We have summarized the toxicity of INH, the successful results of chemo-

prophylaxis trials, and the relative risk of developing tuberculosis, so that the physician can decide in an individual case if INH should be given.

An ideal chemoprophylactic agent should be easy to administer, effective in preventing disease, cheap, and non-toxic.¹ Isoniazid is easy to administer to children and adults. The total cost of administering INH for one year is eighty dollars—infinitely less than the cost of prolonged treatment in hospital for active tuberculosis.² Although unusual, some undesirable effects have been attributed to INH. The drug may induce a syndrome similar to systemic lupus erythematosus or rheumatoid arthritis.³⁻⁶ It increases the cumulative effects of diphenylhydantoin (Dilantin®).⁷ Drug resistance has been reported but is very rare in chemoprophylaxis.⁸ Although only rarely serious, liver toxicity has occurred,^{9,10} and isoniazid chemoprophylaxis should be deferred

From the Medical Service, San Francisco General Hospital, and the Department of Medicine, University of California, San Francisco. (Dr. Jenkins is now with the University Family Medicine Clinic, University of Oklahoma, and Dr. Davidson at the Boston University Medical Center.)

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Reprint requests to: Dr. Frank F. Davidson, University Hospital, Boston University Medical Center, 750 Harrison Avenue, Boston, Ma. 02118.

TABLE 1.—*Tuberculosis Case Rate per 1000 During Medication Year and Subsequent Followup Years in INH and Placebo Groups*¹³

	Medication Year		Followup Years		Time of Followup
	Placebo	INH	Placebo	INH	
Primary TB (children) 2,750 Cases*	22.9	1.4	7.0	2.2	8 years 70% followup
Contacts of Active TB 27,847 Cases	6.2	1.4	16.2	7.4	10 years 98% followup
Mental Institution Patients** 25,210 Cases	1.7	0.2	7.4	3.4	10 years 94% followup
Alaskan Villagers 6,064 Cases	15.2	5.3	30.8	13.8	6 years nearly 100% followup
Adults with inactive TB never previously treated 1,992 Cases	18.0	9.1	45.0	16.1	5 years 97.8% followup

*This includes children with normal x-rays, paratracheal or hilar node enlargement and parenchymal involvement.

**These patients were treated regardless of whether the skin test was negative or positive.

in the presence of active liver disease.¹¹ Impairment of memory has been reported¹² but is definitely not significant^{2,13} and INH does not adversely affect epilepsy.¹³ Peripheral neuropathy is not a problem with the dose used for chemoprophylaxis unless there is associated malnutrition or alcoholism, in which case pyridoxine should be added. Other mild reactions occur in about one percent of patients;¹⁴ however, the incidence is much smaller in children.² The effectiveness of INH in reducing the incidence of tuberculosis has been demonstrated particularly well in the United States Public Health Service Clinical Trials summarized below. These studies are the basis for recommending INH chemoprophylaxis in the United States today.

Animal Trials

In 1953, Ferebee and Palmer¹⁵ treated guinea pigs with isoniazid, 5 mg per kg of body weight per day, for one month before and for two and one half months after large inoculations of virulent tubercle bacilli. At the end of 26 weeks these animals had survived and maintained normal growth patterns whereas the control animals had died. Then, experimentally infected mice and guinea pigs were treated with INH, beginning on the day of injection, for six weeks. One-hundred percent protection was achieved at eight months relative to controls.¹⁶ In these and other animal studies¹⁷ the efficacy of INH in preventing tuberculosis was related to (1) the size of the infective dose, (2) the time between infection and the initiation of treatment (a delay of over fourteen days resulted in poorer results at a given dose), (3) the duration of therapy (the minimal

period for effective therapy was 12 weeks). In another study, monkeys were inoculated with bacilli and at the same time were given INH for the following four to six months. One year later all the monkeys had negative skin tests, suggesting that true infection has actually been prevented.¹⁸ Thus in animals INH was effective for primary prophylaxis in doses as small as 3 mg per kg per day if administered within two weeks of the onset of infection and for a period of at least three months. These studies were the basis for the trials of chemoprophylaxis in clinically-well humans who, because of a positive tuberculin skin test, were presumed to have been exposed to, if not infected with, *M. tuberculosis*.

Clinical Trials

The benefit of INH prophylaxis was then demonstrated in clinical trials by the United States Public Health Service in patients with no clinical evidence of active disease. The trials are summarized in Table 1.

The participants were given INH, approximately 5 mg per kg of body weight per day, or a placebo in double blind fashion to take for one year. X-ray films of the chest were taken at the beginning of the trial and at the end of the medication year. The results are tabulated in terms of case rates of active tuberculosis per 1,000 in placebo and INH groups both during and after the medication year.

The most striking reduction in morbidity from tuberculosis occurred in children with positive skin tests without other evidence of active disease. There was a reduction of 94 percent in the INH group compared with controls during the

medication year and a reduction of 70 percent thereafter. Curry² reported even more dramatic results in San Francisco school children. There was one case of tuberculosis in 2910 children with positive tuberculin reactions who took INH and 25 cases in 1192 children who did not take INH. One reason for the good results in this study appears to have been the careful follow-up of patients during the medication year to ensure that they took the drug.

In household contacts of newly diagnosed cases of tuberculosis and in the trial in the Alaskan villagers one can see, in Table 1, not only the high risk of developing tuberculosis in these populations but also the beneficial effect of INH relative to controls in preventing active disease during and after the medication year. In mental institutions there was a lower overall risk of developing disease but a similar reduction in active cases in the INH group.

The last group in Table 1 included adults who had never been treated with anti-tuberculosis drugs but who had x-ray evidence of "old" or "inactive" disease—namely fibrotic apical lesions or more extensive disease which had not changed for several years. These patients had a high risk of developing active disease, as seen in the case rate of 18.0 cases per thousand in the placebo group (a case rate similar to that in Alaskan Eskimo villages) as opposed to 9.1 cases per 1000 for those given INH. There seems to be little doubt that INH chemoprophylaxis was worth while in these selected populations.

This last group of "inactive" untreated cases deserve particular attention. First, about 80 percent of the new active cases in the United States occur in people with "endogenous" infection—that is, clinically inapparent disease for over one year.²⁴⁻²⁶ Obviously if these patients could be found and treated with INH before active tuberculosis developed, there would be a major reduction in the number of new active cases. Second, since these patients in whom active tuberculosis develops are the principal source of exposure for previously uninfected persons, the logical emphasis for chemoprophylaxis should be in this group. Thus, the Public Health Service has emphasized the eradication of the chief source of new cases and reservoir of infection rather than BCG vaccination of tuberculin-negative (and therefore uninfected) persons who represent only 20 percent of the new cases. The Public Health Service

feels it is easier in the United States to try to identify and treat the reservoir than to vaccinate the huge number of uninfected persons.

Discussion—

Who to Treat with INH for One Year

It is impractical to attempt to skin test and take x-ray films of everyone in the United States, treating all clinically inactive cases with INH for one year and all active cases with additional therapy, desirable as this would be. However, the high-risk groups should be identified and treated, and the Public Health Service data provide information for identifying them.

Obviously, close contacts of persons with active tuberculosis are at high risk and should be treated after appropriate cultures if their skin test converts and should be followed closely, as with any person whose skin test becomes positive. Certain stress factors are associated with a significant risk of developing active tuberculosis in people with positive skin tests. Many of these patients are seen frequently by physicians and the tuberculin status should be known so that INH can be offered to the tuberculin-positive persons. Alcoholism and malnutrition are associated with poor host resistance to tuberculosis. Gastric resection, which many of these patients have had, is also a predisposing factor. Other groups with poor resistance to infection are those with diabetes (particularly if severe and out of control), and those with an impaired immune mechanism. This latter group means not only those with myeloproliferative disorders, but also those being treated with corticosteroids or other immunosuppressive agents. Pregnancy and silicosis also are associated with a high risk of development of the disease.

In the general population, where the principal reservoir of the disease is, the chief high-risk-identifying factors are (1) the infection status judged by the skin test and (2) the presence of abnormalities on chest x-ray studies even though interpreted as inactive. Foremost, a recent conversion to positive reaction in a person known to be tuberculin-negative previously indicated a risk of 5 to 15 percent that clinically active tuberculosis would develop.²⁷ This is a definite indication for INH after cultures are taken.

Likewise, the presence of x-ray abnormalities, even though interpreted as inactive, greatly increases the risk. In patients in mental institutions

with tuberculin skin tests greater than 10 mm induration, the presence of an abnormal (but "inactive") chest x-ray altered the statistical chance of developing active tuberculosis from 0.11 percent, which is quite insignificant, to 1.31 percent.²² Adults who have never had chemotherapy for tuberculosis and who have inactive disease on clinical and radiological grounds have a tuberculosis morbidity rate of about 2 percent per year. In trials with INH "prophylaxis" in these people, the morbidity rate was about 1 percent during the year of chemoprophylaxis, a reduction of 50 percent. Furthermore, the administration of INH for one year reduced the chances of developing active disease in subsequent years from a value of 4.5 percent in the control group to 1.6 percent in the group who had had INH for a year.¹³ Most of these patients have been followed for ten years. This opportunity for preventive treatment must be extended to this group of adults with positive skin tests and "inactive" tuberculosis on clinical radiological grounds because 80 percent of the new active cases came from this reservoir.²⁵⁻²⁷ An alternative of mass bacille Calmette Guerin (BCG) vaccination, which is done in tuberculin negative persons, would not affect this population which is the chief source of new cases.

Conclusions

It seems appropriate to restate the groups who require chemoprophylaxis (300 mg INH per day for one year for adults) based on the recommendations of the United States Public Health Service and the American Thoracic Society.²⁸

1. Persons who are known to have recently converted their skin test.
2. Persons who have had active tuberculosis in the past and have had no drug therapy or inadequate therapy.
3. Persons with healed adult-type pulmonary tuberculosis and a positive skin test.
4. Certain clinical situations in patients with positive skin tests:
 - (a) Patients receiving corticosteroid or immunosuppressive therapy
 - (b) Patients undergoing a partial gastrectomy
 - (c) Patients with lymphoma or leukemia
 - (d) Patients with severe diabetes
 - (e) Patients with silicosis

(f) Patients in the last trimester of pregnancy*

5. Household contacts of active cases if the contact has a positive skin test.
6. Patients under age 20 years who have positive skin tests.

There are two other categories of patients where the indications are not as clear: (1) persons over age 20 years with positive skin test (not recent converters) and normal chest x-ray films (these patients have a risk of about 0.11 percent per year of developing active tuberculosis,²² and (2) persons with clinical conditions where the skin test is unreliable or who are receiving steroid or immunosuppressive therapy. This risk of developing tuberculosis in the latter group is not known but it is undoubtedly increased. The incidence of untoward effects from INH is about 1 percent at the usual doses,¹⁴ and although most of these effects are minor they must be considered in treating patients with a relatively small chance of developing tuberculosis anyway, such as those over 20 years of age with normal chest x-ray films and positive skin tests for many years. It is imperative to know the tuberculin status of patients in these high risk groups. Any physician who treats tuberculosis sees tragic but preventable cases in which skin testing was not done and chemoprophylaxis was not even thought of. Even if a physician elects not to use INH in high risk patients, the awareness of the risk of developing tuberculosis is the physician's responsibility. This is especially important with the increasing use of corticosteroids and immunosuppressive agents. The least the practicing physician can do is to give the benefit of chemoprophylaxis to his own patients whenever it is indicated.

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*There is absolutely no evidence that INH has a detrimental effect on pregnancy if given before or during the pregnancy.¹³ However, since the number of patients studied is small (581), it seems reasonable to recommend prophylaxis only during and after the last trimester.

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STEROIDS IN OPTIC NEURITIS

We feel that optic neuritis is a form of cerebral edema. We feel that steroids used in proper dosage are definitely effective, and that the effect is dose-related and dose-related at massive dose levels, not at the standard levels. We feel steroids are effective because of the immediate effect on pain. This is within 12 hours. You can start the patient at night, as we usually do, and have improvement manifested the following morning. So we are talking about less than 24 hours in most of these patients. You can see the efficacy of steroids in the effect on pain, visual acuity, visual field, color function, and in the appearance of the disc.

You should treat with high doses of steroids—50 mg of prednisone immediately and 25 mg of prednisone every four hours for six doses. We think that patients should be treated for approximately 36 hours and then re-evaluated for an idea of how long treatment should continue. You may be able to stop treatment in 36 hours and certainly in 72 hours. . . . There is no benefit at all from prolonged treatment with steroids. . . .

What we aim to do is abort the acute attack of optic neuritis in the same way that the neurosurgeon aims to remove cerebral edema after a brain concussion or concussion. We want to minimize the residual effects because it is those effects which tend toward progressive optic atrophy and eventually loss of vision, and determine the life cycle of that patient's optic nerve.

—MARTIN LUBOW, M.D., Columbus, Ohio
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Pneumocystis Carinii Pneumonia

Problems in Diagnosis and Therapy in 24 Cases

LAYNE O. GENTRY, M.D., JOEL RUSKIN, M.D., AND
JACK S. REMINGTON, M.D., *Stanford*

■ *Twenty-four instances of Pneumocystis carinii pneumonia were recognized in 23 patients at the Stanford University Hospitals between 1962 and 1970. The affected persons could be broadly characterized as "compromised" hosts. All but one were receiving immunosuppressive drug therapy for such underlying disease as hematopoietic malignant disease, collagen vascular disorder, and organ transplant rejection. The one patient not receiving immunosuppressant medication had congenital dysgammaglobulinemia and suffered two discrete bouts of pneumocystis pneumonia. Most of the patients were concomitantly infected with other "opportunistic" pathogens.*

Open lung biopsy remained the most reliable method of antemortem diagnosis of pneumocystis infection during this eight-year period. It resulted in little morbidity. Unfortunately, direct examination of appropriately stained sputum specimens for cysts was almost uniformly nonproductive.

The majority of patients received specific antipneumocystis drug treatment (pentamidine isethionate or pyrimethamine and sulfadiazine). "Cure" was achieved when institution of therapy was prompt and duration of therapy approached the empirically recommended two-week course.

The fact that pneumocystis pneumonia can be controlled if recognized early is compelling reason to pursue diagnosis of pneumocystosis in an appropriate clinical setting, namely, in patients with impaired host defenses who have pulmonary infection unresponsive to conventional therapy. There is hope that a noninvasive (serological) technique will be developed shortly to simplify identification of this not uncommon cause of diffuse interstitial pneumonitis.

Postgraduate Fellows, Palo Alto Medical Research Foundation and Division of Infectious Diseases, Department of Medicine, Stanford University School of Medicine (Gentry and Ruskin); and Chief, Allergy, Immunology and Infectious Diseases Division, Palo Alto Medical Research Foundation and Associate Professor of Medicine, Division of Infectious Diseases, Stanford University School of Medicine (Remington).

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Reprint requests to: J. S. Remington, M.D., Chief, Allergy, Immunology and Infectious Diseases Division, Palo Alto Medical Research Foundation, 860 Bryant Street, Palo Alto, Ca. 94301.

PNEUMOCYSTIS CARINII may well be the most frequent cause of interstitial pneumonia in patients compromised because of underlying disease or as a result of immunosuppressive chemotherapy.¹ Since this once uniformly lethal infection has recently been shown to respond to drug treatment (pentamidine isethionate),^{2,3} prompt recognition in seriously ill persons is no longer just an academic exercise. Consequently, diverse approaches to diagnosis of the infection have been proposed, although none has proved to be totally satisfactory. Most frustrating remains the inability to work with the parasite *in vitro*. This report summarizes our experience in diagnosis as well as management of 24 instances of Pneumocystis carinii pneumonia in 23 patients at the Stanford University Medical Center over an eight-year period.

Clinical Material

All patients were treated at either the Stanford University Medical Center Hospital or the Palo Alto Veterans Administration Hospital. In 11 cases (Cases 1 to 11, Table 1), the patients were in hospital between 1962 and 1967 and were the subject of a previous report.^{4,5} In 13 cases (Cases 12 to 24, Table 1) the patients were in hospital between November 1967 and October 1970. Case 14 (Table 1) was also reported separately.⁶

Sputum or tracheal aspirates from patients with diffuse interstitial pneumonia were cultured for bacteria and fungi by conventional methods. They were also smeared on microscope slides which were then fixed in 10 percent formalin and stained with Gomori's methenamine silver nitrate. When these measures failed to reveal a cause for the pneumonia, either thoracotomy with lung biopsy or percutaneous needle lung biopsy under fluoroscopic control was performed. Imprint smears from lung biopsy or autopsy material were also stained with methenamine silver.

If an antemortem diagnosis of Pneumocystis carinii infection was made, treatment with pentamidine isethionate, 4 mg per kg of body weight per 24 hours intramuscularly, was begun immediately and continued for 14 days if the patient survived that long.

Results

The pertinent clinical data relating to each of the cases of pneumocystosis in this series are re-

TABLE 2.—Underlying Diseases in 24 Cases of Pneumocystis carinii Pneumonia

Disease	No. Cases
Leukemia, Acute and Chronic	6
Reticulum Cell Sarcoma	5
Hodgkin's Disease	4
Systemic Lupus Erythematosus	3
Transplant Rejection*	3
Congenital Dysgammaglobulinemia	2†
Lymphosarcoma	1

*Two cardiac and one renal
†Two separate infections in the same patient

corded in Table 1. (The number of cases in each category of underlying disease is shown in Table 2.) Twenty-two of the 23 patients were receiving immunosuppressive chemotherapy for periods ranging from three weeks to seven years preceding diagnosis of P. carinii infection. The remaining patient, a child with congenital dysgammaglobulinemia, was not receiving immunosuppressants. Two separate bouts of pneumocystis pneumonia occurred in this patient⁶ (Cases 14 and 18, Table 1). The child first became ill with pneumonia at age nine months. Pneumocystosis was suspected because his male sibling had died two years earlier with pneumocystis disease proved by autopsy. Open lung biopsy confirmed the presence of pneumocystis infection in the child and he responded to a 14-day course of pentamidine therapy. Approximately two and a half years later this same child was again admitted to hospital with pneumonia and a second thoracotomy with lung biopsy was promptly performed. Typical pneumocystis pneumonia was noted in the biopsy specimen and the child was successfully treated with a second 14-day course of pentamidine.

The techniques employed to diagnose pneumocystosis in our patients are listed in Table 3. Open lung biopsy was performed nine times and was positive on each occasion. Thus, in this series there were no instances in which a premortem open lung biopsy was negative and organisms were found at autopsy. In contrast was our experience with closed percutaneous needle biopsy of the lung. This procedure was performed in seven patients, and in three of them no organisms were seen in the biopsy specimen. However, imprint smears of lung tissue obtained at autopsy from these three patients contained many pneumocystis organisms. Moreover, there were no major complications in patients under-

TABLE 1.—Clinical and Laboratory Findings in Immunosuppressed Patients with *Pneumocystis carinii* Pneumonia

Case No.	Age (yrs) Sex	Underlying Disease (duration)	Immunosuppressive Drugs (duration)	Associated Infection†	Diagnosis			Treatment	Outcome & Remarks
					WBC	Silver Stains Sputum	Lung Biopsy		
1	53 (M)	Reticulum cell sarcoma (14 yr)	Prednisone (7 mo) cyclophosphamide methotrexate, vincristine (7 mo)	—	5100	(—)	OB(+)°	P+S,°° Folinic acid	Died 48 hr after treatment began.
2	41 (M)	Reticulum cell sarcoma (8 yr)	Nitrogen mustard, vincristine, cyclophosphamide (4 mo)	Herpes zoster	2600	ND†	ND	—	Autopsy diagnosis.
3	44 (M)	Reticulum cell sarcoma (7 yr)	Prednisone (4 yr) cyclophosphamide, vincristine (4 yr)	—	1500	ND	ND	—	Autopsy diagnosis.
4	58 (M)	Reticulum cell sarcoma (2 yr)	Prednisone (2 mo) cyclophosphamide, vincristine, actinomycin D (2 yr)	—	3300	ND	ND	—	Autopsy diagnosis.
5	13 (F)	Systemic lupus erythematosus (8 yr)	Prednisone (7 yr) cyclophosphamide (2 yr)	<i>Proteus mirabilis</i> bacteremia	6500	(—)	OB(+)°	Pentamidine	Full treatment course. Improvement in pulmonary function. No evidence of pneumocystis at autopsy months later.
6	39 (F)	Systemic lupus erythematosus (5 yr)	Prednisone (5 yr) cyclophosphamide (1 mo)	CMV§ pneumonitis	5000	ND	PC(—)§§	—	Partial pneumothorax—chest tube. Autopsy diagnosis.
7	23 (F)	Systemic lupus erythematosus (3 yr)	Prednisone (3 yr) nitrogen mustard (1 mo)	Candidiasis, disseminated; CMV pneumonitis	21,500	ND	PC(—)	—	Partial pneumothorax—chest tube. Autopsy diagnosis.
8	35 (M)	Hodgkin's disease (15 yr)	Prednisone (4 yr) chlorambucil, vinblastine, cyclophosphamide (7 yr)	—	3200	(—)	OB(+)°	—	Died 72 hr after lung biopsy.
9	34 (F)	Hodgkin's disease (11 yr)	Prednisone (3 mo) cyclophosphamide, vinblastine, methylhydrazine (5 yr)	—	6300	ND	ND	—	Autopsy diagnosis.
10	68 (M)	Chronic lymphatic leukemia (19 mo)	Prednisone (3 mo) chlorambucil (1 yr)	Cryptococcal meningitis	17,000	(—)	OB(+)°	P+S, Folinic acid	Histological evidence of decreased involvement with pneumocystis; no clinical improvement. Died 4 days after therapy began.
11	26 (F)	Renal transplant rejection (2 mo)	Prednisone (2 yr) azathioprine, actinomycin D (2 mo)	Staphylococcal bacteremia	1700	ND	ND	—	Autopsy diagnosis.
12	42 (M)	Cardiac transplantation	ALG# Immuran, prednisone (2 mo)	CMV pneumonitis	2400	(+) (TA¶)	ND	Pentamidine	Died 48 hr after treatment began; pneumocystis in lungs at autopsy.

13	54 (F)	Cardiac transplantation	ALG Immuran, prednisone (2 mo)	E. coli septicemia; CMV & Bacteroides pneumonia; disseminated Aspergillus & Toxoplasma	2800	(-)	ND	-	Died; pneumocystis present both lungs at autopsy.
14*	9 mo (M)	Congenital dys-gammaglobulinemia	-	-	28,000	(-)	OB(+)	Pentamidine	Survived; 14-day course pentamidine; γ -globulin.
15	40 (F)	Reticulum cell sarcoma (2 yr)	Prednisone (2 mo) cyclophosphamide nitrogen mustard chlorambucil (4 mo)	-	1500	(-)	PC(+)	Pentamidine	Died 72 hr after treatment began; pneumocystis present both lungs at autopsy.
16	25 (M)	Hodgkin's disease (4 yr)	Full course irradiation; prednisone (6 mo)	Candida & CMV pneumonitis; disseminated Aspergillus	17,000	(-)	PC(-)	-	Died; pneumocystis present both lungs at autopsy.
17	51 (M)	Chronic lymphatic leukemia (4 yr)	Prednisone (8 mo) chlorambucil (4 yr)	-	13,000 (89% lymphs)	(-)	PC(+)	Pentamidine	Biopsy complicated by pneumothorax, intrapulmonary hemorrhages; died 11 days after treatment began. No pneumocystis at autopsy.
18*	3 (M)	Congenital dysgamma-globulinemia	-	-	15,000	(-)	OB(+)	Pentamidine	Survived second pneumocystis infection 2 yrs after initial episode.
19	50 (M)	Lymphosarcoma (4½ mo)	Prednisone (4 mo) vincristine cyclophosphamide	Streptococcal septicemia	24,000 (90% lymphs)	(-)	OB(+)	Pentamidine	Died 10 days after treatment began; no pneumocystis at autopsy.
20	17 (M)	Acute lymphocytic leukemia (4 mo)	Prednisone (4 mo) methotrexate	-	480	(-)	ND	Pentamidine	Treated without definite diagnosis; died 36 hr after treatment began; no clinical response; pneumocystis in both lungs at autopsy.
21	43 (F)	Chronic myelogenous leukemia (4 yr. 8 mo)	Myleran (4 yr) chlorambucil (6 mo)	Pneumococcal bacteremia	12,000 (2% myelocytes)	(-)	PC(+)	Pentamidine	Partial pneumothorax-chest tube; 14 day course of pentamidine; infiltrates slowly resolved; survived.
22	68 (F)	Chronic lymphocytic leukemia (8 yr)	Prednisone chlorambucil (6 mo)	-	10,000 (78% lymphs)	(-)	PC(+)	Pentamidine	Partial pneumothorax—no tubes required; died 2 days following full course of treatment; no clinical response; <i>P. carinii</i> found at autopsy.
23	16 (M)	Acute lymphocytic leukemia (3 mo)	Cyclophosphamide, vincristine, cytosine arabinoside, prednisone (3 mo)	-	1200 (80% lymphs)	(-)	OB(+)	Pentamidine	Survived; rapid clearing of symptoms.
24	29 (M)	Hodgkin's disease (9 mo)	Prednisone cytosine arabinoside (8 day)	-	2800	(-)	OB(+)	Pentamidine	Died 6 days after treatment began; no <i>P. carinii</i> found at autopsy.

*Open lung biopsy

**Pyrimethamine & sulfadiazine

†Positive cultures or histopathologic evidence

‡Not done

§Cytomegalovirus

§§Percutaneous lung biopsy

¶Tracheal aspiration done at the time of tracheotomy

#Antilymphocyte globulin

*Cases 14 and 18 were in same patient

TABLE 3.—*Diagnostic Procedures in 24 Cases of Pneumocystitis carinii Pneumonia*

Procedure	No. Times Performed	Procedures Positive	Major Complications*
Open Lung Biopsy	9	9	0
Closed Needle Lung Biopsy	7	4	3
Silver Stains of Sputum	17	1	0
Initial Diagnosis at Autopsy	—	10	—

*Greater than 20 percent pneumothorax or intrapulmonary hemorrhage

going an open biopsy procedure (Table 3). However, three patients who had a closed needle biopsy had either significant pneumothorax (greater than 20 percent) requiring a chest tube or significant intrapulmonary hemorrhage. In one patient complications following the needle biopsy were in large part responsible for his death.

Examination of sputum smears proved to be unrewarding in diagnosis of *P. carinii* pneumonia (Table 3). Only one positive specimen was obtained. This was aspirated from a tracheostomy site in a cardiac transplant patient (Case 12, Table 1). Sputa from 17 of the patients were examined more than once and were consistently negative.

In ten patients the diagnosis of pneumocystis pneumonia was established only at autopsy (Table 3). In four of these ten (Cases 4, 9, 12 and 20, Table 1), the diagnosis was suspected premortem, but biopsy was not performed because these patients were felt to be at the terminal point of their underlying disease. Two of these patients (Cases 12 and 20, Table 1) empirically received antipneumocystis therapy. Two of three patients receiving immunosuppressant drugs for organ transplant rejection died of unsuspected *P. carinii* pneumonia. However, one of these, a renal transplant recipient (Case 11, Table 1), had concurrent bacteremia due to *Staphylococcus aureus*. The other patient, a cardiac transplant recipient (Case 13, Table 1), had concurrent infections with *E. coli*, *Bacteroides*, *Aspergillus*, *Toxoplasma*, and *Cytomegalovirus*.⁷

Because *P. carinii* has been found in tissues other than lung (spleen, liver, bone marrow, and lymph node),⁸ silver stains of these tissues were examined in six selected patients in this series. No extrapulmonary organisms could be demonstrated.

TABLE 4.—*Concomitant Infections in 11 Patients with Pneumocystitis carinii Pneumonia*

Case No.	Infections
2	Herpes Zoster—Severe Skin Involvement
5	<i>Proteus Mirabilis</i> Bacteremia
6	Cytomegalovirus Infection both Lungs
7	Cytomegalovirus Infection both Lungs, Disseminated Candidiasis (Kidneys, Lungs, Liver and Spleen)
10	Cryptococcal Meningitis
11	Staphylococcal Bacteremia
12	Cytomegalovirus Infection both Lungs
13	<i>E. Coli</i> Septicemia, Cytomegalovirus Infection both Lungs, <i>Bacteroides</i> Infection Left Lung, Disseminated <i>Aspergillus</i> Infection, <i>Toxoplasma</i> Infection of Heart and Brain
16	<i>Candida</i> Infection Left Lung, Disseminated <i>Aspergillus</i> Infection, Cytomegalovirus Infection both Lungs and Liver
19	Streptococcal Bacteremia
21	Pneumococcal Bacteremia

Pneumocystis pneumonia was accompanied by other infections in 11 of the patients (Table 4). Infection with virus (for example, herpes zoster or Cytomegalovirus) either alone or in combination with other infectious agents was encountered in six patients. Bacterial septicemia occurred in five patients, but in four of them positive blood cultures were not detected until after the patients had died. Severe fungus infections with *Aspergillus*, *Candida* or *Cryptococcus* were encountered in four patients and mixed fungus or fungus together with virus infections were common. Disseminated toxoplasmosis was unsuspected in a cardiac transplant patient and, as noted above, it occurred in combination with four other infectious agents.

Twelve courses of pentamidine isethionate and two courses of pyrimethamine and sulfadiazine were administered in this series for periods ranging from one to fourteen days (Table 5). Five patients survived. Each received pentamidine for at least nine days, and all but one (Case 23, Table 1) received a full 14-day course. This latter patient showed rapid clinical improvement, but the drug was discontinued after the ninth day of therapy because of elevated blood urea nitrogen. The patient continued to improve, and the blood urea nitrogen level returned to normal within three days. Among the four remaining successfully treated cases were the two episodes of *P. carinii* pneumonia occurring in the same patient (Cases 14 and 18, Table 1) with congen-

TABLE 5.—Results of Therapy in 14 Cases of *Pneumocystis Pneumonia*

Results	No. Cases	Treatment Period (days)	
		1-9	10-14
Equivocal or No Clinical Response; Patient Expired; <i>P. carinii</i> Present at Autopsy	6*	5	1
Clinical Response; Death before Therapy Completed; <i>P. carinii</i> Not Present at Autopsy	3	1	2
Clinical Response; Completed Therapy	5	—	5

*Includes 2 patients treated with pyrimethamine and sulfadiazine.

ital dysgammaglobulinemia. To our knowledge, this is the first instance of successful treatment of two separate bouts of *P. carinii* pneumonia with pentamidine.

Three patients treated with pentamidine improved clinically but died before a full course of therapy was completed. One patient (Case 24, Table 1) died on the sixth day of pentamidine therapy. Initial clinical improvement was followed by increasing respiratory distress and death. At autopsy there was interstitial pneumonitis with extensive intra-alveolar proteinaceous debris in both lungs, but no *P. carinii* were seen. Another patient (Case 19, Table 1) had recurrence of pulmonary decompensation after initial improvement and died on the tenth day of pentamidine treatment. No *P. carinii* were found at autopsy in this patient either, but he too had severe bilateral interstitial pneumonitis. A third patient (Case 17, Table 1) died on the eleventh day of pentamidine therapy. The diagnosis of *P. carinii* in this case was made by percutaneous needle lung biopsy. Pneumothorax followed the biopsy, and, despite treatment with a chest tube, the patient died with recurrent pneumothorax and subsequent respiratory arrest. There was clinical and radiographic evidence of improvement in the interstitial pneumonia during the 11 days of therapy with pentamidine, and at autopsy no parasites were noted. However, a large area of pneumothorax was present as well as extensive intrapulmonary hemorrhage at the site of the needle biopsy.

Four patients receiving pentamidine had no observable clinical response. Three of them died within three days after the beginning of therapy. At autopsy each had severe interstitial pneumonia with large numbers of *P. carinii* present

in the involved lung tissue. The fourth patient, in whom no detectable therapeutic effect of the drug was observed, had an atypical clinical response. This patient (Case 22, Table 1) had a percutaneous needle lung biopsy (positive for *P. carinii*) performed early in the course of interstitial pneumonia. Pentamidine therapy was begun and continued for 14 days. There was no improvement in the roentgenographic findings during this time and, while she was receiving pentamidine, progressive respiratory distress developed. She died of anoxia on the second day following a full 14-day course of the drug. At autopsy there was severe interstitial pneumonia in both lungs, associated with large numbers of *P. carinii*.

Because pyrimethamine and sulfadiazine were known to be effective in treating *P. carinii* pneumonia in experimental animals⁹ and since pentamidine isethionate was not readily available before 1967, two patients (Cases 1 and 10, Table 1) were treated with this combination. The results were equivocal, as reported previously.^{5,10}

Discussion

Pneumocystis carinii pneumonia has been well documented as a disease entity in patients receiving immunosuppressive chemotherapy for underlying diseases and in children with immunologic deficiency syndromes.^{4,5,11,12,13} The 24 episodes of pneumocystosis described in this report occurred in similar clinical settings. Each of the patients had received immunosuppressive drugs except for the child who had hypogammaglobulinemia. Undoubtedly, the type and severity of underlying disease are important factors in the pathogenesis of this infection. However, it is difficult to quantitate these factors, and no such assessment was possible in this series.

Although reports of finding *P. carinii* in normal lung tissue at autopsy are rare,¹⁴ recent studies in Europe and the Middle East, utilizing direct sputum examination and serologic techniques, suggest that the carriage rate of pneumocystis in children may be as high as 40 percent.¹⁵ These data support the hypothesis that clinical *P. carinii* infection in the "compromised" host is almost always due to activation of latent infestation rather than to exogenous infection.⁴ Because methenamine silver staining of lung tissue obtained at autopsy has not been done

routinely at the Stanford Medical Center, no statistics are available as to the actual incidence of the organism in our hospital population.

Open lung biopsy has been proposed as a safe and most reliable method for obtaining representative tissue in diffuse pulmonary disease.^{16,17} This method was used nine times in our series, with success in all instances. Selection of maximally involved tissue for biopsy may in part be responsible for this result. The most frequently reported complications of the procedure, pneumothorax, bleeding and infection,¹⁶ did not occur. The absence of complications in this series and in others may have been due to rigorous clinical evaluation of patients before biopsy. Potentially troublesome underlying problems were either detected and corrected before operation or biopsy was not performed because the risk to the patient was deemed too great.

Recent reports in the literature suggest that closed needle lung aspiration may also be useful in the diagnosis of *P. carinii* pneumonia.^{18,19,20} The fact that three of seven patients who underwent closed needle biopsy in this series had major complications (which may have led to the death of one patient) is in definite contrast to data from most reported studies. Most disturbing in this series was the failure of the closed lung biopsy specimen to disclose *P. carinii* in three of seven patients in whom the diagnosis was ultimately proven at autopsy. In these three, there was severe diffuse bilateral interstitial disease documented radiographically, and the biopsy specimen was taken from what was considered to be severely involved lung tissue. None of our patients had repeat needle biopsy, and reports in the literature suggest that this may be necessary to obtain a diagnosis.²¹ Sampling error may have been responsible for the negative results in the three cases described above. Clinical conditions did not permit antemortem open lung biopsy in these individuals. Such a controlled study is necessary to compare the relative accuracy of the two diagnostic procedures.

Serological methods for recognition of *P. carinii* have had sporadic use, especially in Europe. A complement fixation test that employs infected human lung tissue as antigen has been reported to be positive in up to 90 percent of children with pneumocystosis.²² Impurity of the antigen is a major problem with this procedure. Immunofluorescent techniques have also been utilized

successfully to demonstrate *P. carinii* in lung tissue sections.^{23,24} However, routine fluorescent antibody testing for the infection is not yet practicable because no uniform method has been adopted for preparing pneumocystis antigen in large quantity.

In work to be reported separately we have investigated an immunofluorescent diagnostic technique which employs pneumocystis antigen derived from rat rather than human sources. Since heavy pulmonary infection with pneumocystis can be induced almost uniformly in Sprague-Dawley rats treated with cortisone,⁹ we believe the rat model would provide laboratories with both a standard and readily available reservoir of antigenic material. Imprint smears of cut surfaces of pneumocystis-infected rat lungs made on clean microscope slides, air dried, fixed in ethanol and stored, if desired, at -20° have proved to be an effective and reproducible antigen in an indirect fluorescent antibody test. (The lung antigen may be obtained from animals soon after death or from tissue previously frozen at -70° C for up to two months.)

A variety of sera were tested by this method in our laboratory. The sera came from normal and overtly infected humans (four of these were from early patients in our Stanford series); from normal, "germ-free" and overtly infected rats; and from rabbits previously immunized with rat alveolar lavage aspirates containing large numbers of pneumocystis organisms or with emulsions of minced human or rat lungs infected with the organism. A number of different fluorescein-conjugated antisera were evaluated as well.

The results of the study, although incomplete, suggest that the technique may be of distinct value in diagnosis of pneumocystis infection, since immunofluorescent structures similar morphologically to silver-stained cysts (and possibly trophozoites) of *P. carinii* have consistently been observed. But the test has not been developed to the point where sera from grossly infected individuals can be entirely segregated from "control" sera on the basis of intensity of fluorescence. The reason for this may lie in the fact that the method is not sensitive enough to detect antibody titer differences in sera derived from clinically infected hosts and "controls" who, in fact, may also be infected, though subclinically, with the parasite.

The efficacy of pentamidine isethionate in the treatment of *P. carinii* pneumonia has been well documented.³ Evidence from our series and others further reveals that efficacy is directly related to rapid diagnosis and early treatment. In the five instances of recovery in our group of patients, the diagnosis was suspected immediately. Survival appears to be related also to duration of pentamidine therapy. In this series all five surviving patients received at least nine days of pentamidine, and in one other large series an average of ten days of treatment appeared to have a positive correlation with survival.³

It is difficult to assess the role of underlying disease in trying to evaluate effectiveness of pentamidine or other chemotherapeutic agents in pneumocystosis. Patients with acute leukemia have been noted to have a high mortality in other reported series of *P. carinii* infection.²⁰ The results in our patients were consistent with this finding. Persons without rapidly fatal underlying disease might be expected to have a better outcome. In particular, the child with congenital dysgammaglobulinemia in our series fits this latter category. He was treated successfully with pentamidine for two separate episodes of *P. carinii* pneumonia two years apart.⁶

Side effects following administration of pentamidine have been reported to include both local and systemic reactions.³ Mild reversible azotemia and hypoglycemia have been encountered most frequently. Although these systemic reactions occurred in this series, they did not produce serious complications.

Because alternative effective drugs for the treatment of *P. carinii* infections are limited, one instance (Case 22) of pentamidine failure encountered in this series was particularly disturbing. The patient died of respiratory insufficiency despite a full 14-day course of the drug. The fact that numerous *P. carinii* were present in the lung at autopsy suggests that either the patient had overwhelming infection or that the strain of *P. carinii* was resistant to pentamidine. Because the organism has not been grown *in vitro*, such resistance cannot be proved. Although cases of pentamidine failure have been recorded,^{1,3} most deaths have occurred early in the course of the disease rather than after treatment has been completed.

The efficacy of a combination of pyrimethamine and sulfadiazine in treatment of pneumocystosis has been shown in certain animal studies.⁹ Before pentamidine isethionate became available, two of our patients were treated with these two agents. Although both patients died, in one there was histological evidence at autopsy of regression of infection.⁵ After pentamidine was made available through the Parasitic Drug Service of the National Center for Disease Control, none of our patients was treated with pyrimethamine and sulfadiazine. However, controlled studies comparing the two different drug regimens would be of value, especially now that an intravenous form of pyrimethamine is available from Burroughs-Wellcome.

Consistent with reports of other investigators is the increased incidence of concomitant infections in our patients with pneumocystosis. Infections with viruses, fungi and bacteria are common in patients with the underlying diseases which are also associated with *P. carinii*, making any conclusions as to the significance of their association with pneumocystosis difficult. There is no proof that any of these opportunistic infectious agents potentiates development of the others.

Because clinical experience with *P. carinii* in the United States has been limited to the last decade, there is inadequate knowledge of the host-parasite relationship in this disease. In infections caused by bacteria, fungi, viruses and other protozoa, specific animal models have been adapted to quantitate number of organisms and route of inoculation necessary to produce disease of various organs. Because *P. carinii* has not been adapted to *in vitro* culture techniques, no experimental challenge studies with this parasite are available. Thus, there are no guides as to number of organisms necessary to cause disease. Clinical experience with several patients in this series further illustrates how this lack of knowledge makes it difficult to evaluate severity of infection in each patient. In several patients, there were large numbers of parasites present in all alveoli on biopsy, yet their response to drug therapy was rapid; whereas in others, whose biopsy specimens contained very few parasites, the clinical picture was that of overwhelming infection. In several instances, patients with totally different clinical courses had similar underlying disease and had received comparable immuno-

suppressive chemotherapy. Thus, further studies of host-parasite interaction and virulence of the parasite are crucial to improved understanding of this unusual infectious process. These studies must await development of more sophisticated culture techniques and an *in vitro* model.

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USE OF ANTIBIOTICS IN TREATMENT OF HUMAN AND DOG BITES

Probably the dirtiest part of the human body is the mouth—not only by verbal response but by culture! One can never be sure what grows there.

In human and dog bites, our advice is to leave the wound open. We save some problems by doing this. We start with a double scrub; we scrub the wound for 15 minutes and then we discard and redrape and double scrub again for ten minutes, a classic surgical preparation. Then in terms of antibiotics, we start with the penicillin A's, usually oxacillin, 500 mg every six hours on an outpatient basis. I think that the penicillin we have been using has been the phenoxymethyl type. If the patient has to be hospitalized, we use 10 to 15 million units intravenously over a 24-hour period. After two or three days the wound, if it is clean, is closed. The Gram stain will tell you whether you need to add an agent specific for some of the negative organisms, the hemophilus and fusiform bacteria. But it's the combination of the spirochetes, the hemophilus, and the fusiforms that really get you into trouble. These should be treated very cautiously. Even in the phase where most other wounds heal quite nicely, dog and human bites are a very treacherous type of injury. We admit all patients with human bites, especially of the hand or face, leave the wounds open and treat them in this manner.

—DAVID R. BOYD, M.D., Chicago
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Endarterectomy of the Internal Carotid Artery

O. G. DAVIES, JR., M.D., J. D. THORBURN, M.D., AND
PARKER POWELL, M.D., Fresno

■ *Results of 219 operations in 171 patients for arteriosclerotic stenosis of the internal carotid artery were consistently good in patients with lateralizing, transient ischemic attacks. Although less consistent, relief of symptoms may be expected in a high proportion of patients with significant stenosis and more nonspecific symptoms. A small number of patients (10 percent) may have significant stenosis without a bruit. Asymptomatic stenosis, which has an unpredictable prognosis, may be operated upon with low mortality and morbidity. The use of local anesthesia and shunting when necessary proved to be the safest technique for the authors.*

DESPITE AN EVER GROWING NUMBER of reports on the surgical treatment of carotid artery stenosis due to arteriosclerosis, there still remains considerable difference of opinion regarding diagnosis, indications for treatment, and the technique of surgical correction. The purpose of this report is to present a method of management in these disputed areas. In the series being analyzed, there were 219 sides operated upon in 171 patients. The age distribution was from 39 to 83 years, and there was a slight preponderance of male over female patients (85 and 73 respectively). These patients were all operated upon, by one of the three authors, consecutively from 1959 through 1970.

Diagnosis and Presenting Complaints

There has been little attempt to correlate the results in surgically treated patients with the variable presenting symptoms which may be attributed to the cerebral ischemia. It was apparent in this series that certain symptoms—namely headache, syncope, confusion, memory loss, dizzy

spells, visual disturbances, tinnitus, hearing disturbance, and numbness—were nonspecific symptoms and may or may not be a result of vascular insufficiency.

When one examines the results as to relief of the presenting symptom in patients with carotid artery stenosis, it is notable that patients with classical transient ischemic attacks and lateralizing signs have consistently better results than those with less specific symptoms.

In this series of patients, there were 79 who presented with what was considered typical symptoms of transient, unilateral weakness, speech impairment and varying degrees of syncope. In 56 patients, the symptoms were classified in the nonspecific category. Although the symptoms in these patients were compatible with cerebral ischemia, they could also have been due to other causes such as primary ear or eye disease, epilepsy or heart block. Nine patients were operated upon within two weeks of the development of an acute stroke. The degree of neurologic deficit was "fixed" at the time of operation. In 27 patients the stenosis was asymptomatic and was noted incidental to ex-

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Reprint requests to: O. G. Davies, M.D., 159 North Thesta Street, Fresno, Ca. 93701.

amination for other causes. Often, these patients had disabling vascular disease elsewhere requiring repair, and it was felt that the carotid stenosis should be corrected before other major operation was undertaken. Some of the patients were in good health and were noted to have a bruit incidental to routine physical examinations. All the asymptomatic patients underwent endarterectomy without complications and remained asymptomatic.

Although some data are available regarding the prognosis of the untreated patient with transient ischemic attacks,^{1,2} it is impossible to say what the outcome would have been without surgical intervention for the asymptomatic patients. Since it is not unusual that major stroke is the first manifestation of internal carotid occlusion, perhaps some of these patients would have had neurologic deficit if total occlusion had taken place.

Physical Findings

The most valuable diagnostic sign indicating stenosis was the presence of a bruit over the carotid bulb.³ However, there were 21 patients in the series (approximately 10 percent) studied by arteriography who, in spite of the absence of carotid bruits, proved to have narrowing of the vessel of 50 percent or greater. We believe that arteriograms should be obtained even in the absence of a bruit if the clinical history is typical but that such studies may be withheld if the symptoms are vague. Since provocative testing by compressing the vessels is inconclusive and may be dangerous,⁴ we do not use it as a diagnostic maneuver. Most of these patients showed an absence of neurological deficit at the time of operation, although an occasional patient with chronic neurologic deficit has shown favorable response to carotid endarterectomy. Ophthalmodynamometry studies were done in several patients in the early part of the series but the results were too equivocal to be of any value as a screening procedure.

X-ray Examination

Rather than use a standard method for each examination, we tailored the method of arteriography to the patient's condition. In the early part of the series, open and percutaneous direct injection of contrast media into the common

carotid artery was the method. Direct exposure of the vessel was used in preference to percutaneous injection since it lessened subintimal injection and at subsequent operation we found less perivascular reaction due to leakage at the needle puncture site. Arch studies were used in instances where there were bruits over the vessels at the arch, or the symptoms suggested posterior brain involvement, or blood pressure differentials were present. More recently, catheterization of individual vessels by way of the arch catheter provided the same clarity of visualization without incurring the risk of direct percutaneous injection of the carotid arteries. Direct injection of the carotid arteries may be required in situations where the arch catheter (passed by either the femoral or subclavian routes) cannot be manipulated to provide selective injection of the carotid arteries.

Timing of Operation

In four patients treated early in the series, "strokes" of severe magnitude had occurred within the first 24 hours following x-ray study. Three of these occurred in the recovery room shortly after study. The patients were returned to the operating room and endarterectomy of the vessel was done within a half hour of the onset of symptoms. In all of these patients there was progression of neurologic findings, with coma and death in two cases. This experience, together with that of other observers^{5,6,7} led to the conclusion that it is unwise and dangerous to revascularize the fixed "stroke" in the acute phase. If the symptoms of the acute "stroke" clear promptly, the brain is merely blanched but not infarcted and early revascularization is imperative. We believe that if the process resolves in the first day or two, these are reversible changes in the tissue. The patient in these precarious circumstances, who is fading in and out of neurologic deficit, is taken directly to the operating room for emergency endarterectomy, but first the carotid bulb is exposed and x-ray examination with a single cassette is done to confirm the stenosis (Figure 1).

Surgical Technique

As the literature indicates, there is considerable controversy regarding methods of protecting the brain during the period of occlusion.

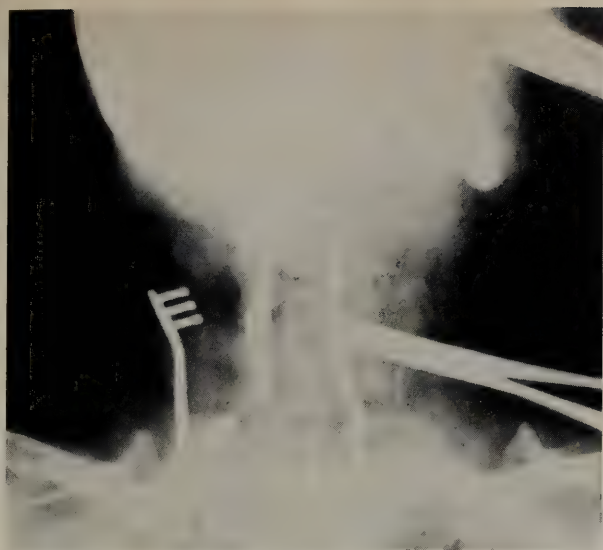


Figure 1.—Single exposure, taken in operating room, of patient in precarious condition.

Although general anesthesia is known to lower cerebral metabolism, other adjuncts must be added to insure adequate brain protection. Hypothermia, "stump" pressure measurement, routine shunting of the vessel under general anesthesia, hypercarbia and hypocarbia have all been proposed and utilized.^{8,9} It is the authors' opinion that no method of brain monitoring can be as accurate as utilizing the patient's own clinical response. With general anesthetic of any type this vital indicator of function is lost. In the first six patients in this series, general anesthesia and hypothermia were used without incident. However, the sixth patient awoke with partial hemiparesis in spite of quite adequate reduction of body temperature. Since then, all patients have been operated upon under local anesthesia. The patient is given 35 to 50 mg of heparin intra-arterially and all branches occluded for three minutes. Patients who cannot tolerate the occlusion rapidly become confused, hemiparetic, or unconscious. An internal shunt is then used and the operation completed around this bypass. Once testing has been accomplished, the supplemental use of fentanyl (Innovar®) has been very helpful for restless patients. Since shunting was necessary in only 35 patients (16 percent), use of the order of procedure here described permitted limiting treatment in 84 percent of cases to this rather simple, rapid and safe operation. Patching of the repair site was found unnecessary, for the vessel at the endarterectomy site is actually large in caliber following careful



Figure 2.—After endarterectomy (same patient as in Figure 1), showing no need for "patching."

closure (Figures 1 and 2). It has been noted that the incidence of thrombosis is no different with than without patching, and that leaving an aneurysmal dilatation is as bad as a constricted area from a hemodynamic point of view.

Results

In this series of 219 sides in 171 patients, there were seven postoperative deaths in hospital. Two were due to acute myocardial infarction. Two occurred in patients operated upon in emergency for acute "fixed strokes," an operation the authors now believe is inadvisable. Three patients had acute thrombosis at the operative site and died in the early postoperative period. (It should be noted also that reoperation in the acute phase in two of these patients probably brought on additional brain damage.) The total operative mortality was 3.2 percent; but if the two patients with the fixed strokes are excluded, operative mortality was 2.3 percent, which is in keeping with that reported by others.^{6,8-10} There were 25 late deaths in the series, 23 due to myocardial infarction, one to malignant disease and one incidental to other major vascular operation. Only two patients have shown late worsening of preexisting neurologic deficit. It was of interest that there were no late deaths due to "strokes."

In the cases in which bilateral studies were done there were 14 instances of total occlusion on one side associated with pronounced stenosis on the other. The patients all did well following endarterectomy on the stenotic side, and there has been only one late death among them, it due to myocardial infarction.

Contrary to the conclusions of the joint study,¹⁰ the authors would feel that this group of patients urgently need correction of the stenotic side and that without operation the outlook is poor.

The patients surviving the operation were placed in three categories for analysis:

GROUP ONE—Improved. Patients with typical lateralizing “small stroke” symptoms preoperatively or with the described “atypical” symptoms which had cleared and without further attacks; or patients with late residual neurologic deficit preoperatively that cleared or improved postoperatively. Total 95.

GROUP TWO—Worsened. Patients who survived but had or later developed more neurologic deficit than preoperatively. Total 6. In one case these complications occurred under hypothermia.

GROUP THREE—Unchanged. Status remains the same as before operation; hence the value of the operation to the patient is undetermined. These include 27 patients who were asymptomatic before and remained so after operation. There were five patients who had “fixed strokes” and residual paralysis and their condition remained unchanged postoperatively. There were 28 patients whose symptoms were of the ill-defined category and continued so after operation. Total 60.

There were three patients lost to follow-up examination six months to two years postoperatively.

Conclusion

- Arteriosclerotic stenosis of the internal carotid artery of sufficient degree to produce symptoms is often a clear-cut clinical syndrome consisting of contralateral transient hemiparesis with speech impairment and an associated bruit over the carotid bulb. In this group of patients, one can expect the best results postoperatively.

- The stenotic artery may also be associated with more diffuse and nonspecific symptoms of neurologic deficit. However, since other conditions may be acting to produce these symptoms, the result in this group of patients is less predictable.

- A small proportion of patients may have significant stenosis without bruits; hence study is indicated if the symptoms are typical.

- The asymptomatic stenosis has an unpredictable prognosis and may be surgically treated with low morbidity and mortality.

ADDENDUM: In the interval since the manuscript was prepared, 42 patients have undergone a total of 53 operated sides without additional mortality or morbidity.

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ALL THAT WASHES DOES NOT CLEAN

Even such well-known drug incompatibilities as pHisoHex®, which is an anionic detergent, and Zephiran®, which is a cationic detergent, are commonly disregarded. It's not unusual to find surgical scrubs with a mixture of these two detergents which actually neutralize each other rather than enhance each other.

—WILLIAM HAVENER, M.D., Columbus, Ohio
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Diagnosis of Immunologic Deficiency In Childhood

PAUL J. EDELSON, M.D., *San Francisco*

■ *A defective host response may be responsible for recurring infections in certain children. Recognition of these defects may be important both therapeutically for the patient and for genetic counseling for the family. Family history, age of onset of illness and type of infecting agents may all point to one or another defect in host resistance.*

An initial evaluation for suspected immunologic disease may be rapidly accomplished and should include absolute neutrophil and lymphocyte counts, chest X-ray for a thymic shadow, Schick test for functional IgG antibodies and isohemagglutinin titers for functional IgM antibodies. Although serum protein electrophoresis is unreliable for diagnosis of most disorders of circulating antibodies, quantitation of the IgG, IgA and IgM antibody classes is generally available. More extensive studies may be carried out to further define defects in the cell-mediated immune system, in the various complement components, or in the ingestion and killing of bacteria by neutrophils.

A PATIENT, PARTICULARLY A CHILD, with a history of repeated infection presents a frequent, often difficult and at times urgent, diagnostic challenge for the physician. A mere history of repeated superficial infections does not necessarily indicate an inadequacy of the child's immune system, for during the first four or five years of life children must acquire a "library of immunity" to a large number of viral and bacterial agents, accomplishing much of this through clinical infection. However, a child whose infections are

chronic, or recur regularly, and are deep or disseminated, deserves special attention. If a congenital defect of the immune system should be present, diagnosis becomes essential not only for therapy of the child, but also in many cases for genetic counseling of the family.

The physician's immunologic pharmacopia has been recently expanded from specific anti-toxin and human gamma globulin preparations to include transplantation of genetically acceptable bone marrow,¹ embryologic lymphoid and thymic tissue,² and immunologically specific transfer factors.³ These specific therapies make the early, accurate diagnosis of the immunologically incomplete individual more urgent. They also result in a need for precise identification of chil-

From the Section of Hematology and Immunology, Department of Medicine, University of California, San Francisco.

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Reprint requests to: P. J. Edelson, M.D., Section of Hematology and Immunology, Department of Medicine, University of California, San Francisco, San Francisco, Ca. 94122.

TABLE 1.—Approach to Diagnosis of Immunologic Dysfunction—Specialized History and Physical Examination

<i>Immunoglobulin Deficiency</i>	<i>Defective Cellular Immunity</i>	<i>Non-Specific Host Defenses</i>	<i>Local and Anatomic Disorders</i>
<i>Initial Work-up</i>	<i>Initial Work-up</i>	<i>Initial Work-up</i>	<i>Initial Work-up</i>
—IgM antibodies: isohemagglutinin titers	—skin tests:	—Absolute neutrophil counts (on several occasions)	—Cystic fibrosis: sweat test
—IgG antibodies: Schick test	—PPD	—Splenic function: Howell-Jolly bodies	—Recurring urinary tract infec- tions: IVP
—X-ray: soft-tissue neck for lymphoid tissue	—Mumps		—Recurring meningitis; studies for skull, mid-line defects
	—Absolute lymphocyte counts (on several occasions)		—Protein-losing malabsorption states: serum albumin level
<i>Confirm with</i>	<i>Confirm with</i>	<i>Confirm with</i>	
—Specific immunoglobulin levels	—PHA stimulation of lymphocytes	—Spleen scan	
—Specific titers after antigenic stimulation	—Uncommon antigens for initial stimulation	—NBT test	
—Regional lymph node biopsy		—Quantitative comple- ment level	
		—Other research tests for complement function	
		—Specialized studies of neutrophil function	

dren who have recurrent superficial infections but who have full immunologic function and who may require no treatment other than reassurance.

Children whose recurring infections represent a localized, or non-immunologic underlying defect may often be identified by a history of infection limited to a specific anatomic locale. Urinary tract anomalies, anatomic defects leading to repeated meningitis, or the suppurative pulmonary complications of cystic fibrosis, as examples, produce their own specific constellation of problems. A child with a disorder of this sort does not need immunologic investigation. A sweat test, skull films for occult mastoid or cribriform plate fractures, or intravenous pyelograms are more appropriate.

If, however, a broader immune defect is suspected, it becomes important to determine which protective responses are impaired, as the results of such a work-up may carry therapeutic implications for the patient and genetic implications for his family. Current theory pictures host defenses as composed of specific and non-specific responses. Non-specific responses include the ability of white cells to digest and kill bacteria and fungi,⁴ as well as such non-specific protective serum components as lysozyme and the complement system.⁵ The specific immune system is further divided into the circulating serum

antibodies, and cell-mediated responses dependent upon the small lymphocytes.⁶ The former are the classical antibodies, while the latter are responsible for such "delayed type" reactions as the tuberculin skin reaction or the rejection of foreign tissues. In evaluating a child for an immunologic deficiency, each of these several host factors must be considered. (See Table 1.)

History

A family history is of key importance, as many of these diseases are genetically determined. The pattern of illness in affected relatives may be a clue to the specific disorder of the patient himself. Evidence of specific involvement of maternal uncles or cousins strongly suggests an X-linked disorder, such as the Bruton-type of hypogammaglobulinemia,⁷ X-linked thymic dysplasia,⁸ or certain varieties of chronic granulomatous disease.⁹ A pattern involving siblings of both sexes without involvement of other family members, may indicate an autosomal recessive disorder. A history of consanguinity may also suggest a recessively inherited disorder. In many, perhaps a majority of cases, however, no identifiable family pattern of inheritance is present, even when the disease has a genetic basis. This may be because of lack of complete information about highly mobile families or perhaps because the disease results from a new mutational event.

The age of onset of illness serves to differentiate such early appearing defects as "Swiss-type" thymic alymphoplasia,¹⁰ and the DiGeorge syndrome (absence of the thymus and parathyroid glands¹¹) which become symptomatic very early in infancy, from the Bruton-type hypogammaglobulinemia which usually becomes symptomatic in the second half of the first year of life, as the placentally acquired reserve of maternal antibodies is exhausted. The history of a long period of good health followed by the development of recurrent infections later in childhood may indicate an acquired, rather than a congenital, immune defect.

The type of infecting micro-organisms may also be of diagnostic significance. Children with hypogammaglobulinemia or a defect in phagocytosis are likely to have had little problem with viral infections or live virus immunizations, whereas infection with pneumococci or Hemophilus influenza may be devastating. On the other hand a child with defective cellular defenses may receive a live poliomyelitis or vaccinia virus vaccine with fatal consequences. In such a child, ordinarily mild childhood diseases like measles, or varicella, may progress to such life threatening complications as pneumonia, myocarditis or hepatic necrosis. If any of the child's siblings have experienced any of these complications of immunization or natural infection, live virus immunizations should be withheld until his immunologic status has been carefully explored.

Physical Examination

Physical examination of the child who may be immunologically deficient should be directed toward answering three major questions.

- *Are signs of chronic infection present?* Chronic mucocutaneous candidiasis, chronically draining ears, or multiple abscesses all may indicate a basic disorder of the host's defenses.

- *What is the status of the visible or palpable lymphoid organs?* Obvious lymphadenopathy or enlarged tonsils are less likely to represent an immune deficiency state than is scantiness or absence of lymphoid tissue.

- *Are associated physical signs present which suggest a specific immunologic diagnosis?* The hypocalcemic tetany, cardiac anomalies and hypoplastic mandible of DiGeorge's syndrome, the ocular and cutaneous telangiectases of ataxia-telangiectasia,¹² or the partial albinism of the

Chediak-Higashi syndrome¹³ all may alert the pediatrician to an underlying immune defect. Children with congenital hypogammaglobulinemia may occasionally present with an arthritis indistinguishable from rheumatoid arthritis.¹⁴ And in one of the few syndromes of immune deficiency of known cause, we have learned to look for signs of defective immunity in infants with congenital rubella.¹⁵ Such infants may present in the newborn period with cellular immune defects along with the thrombocytopenia and hepatosplenomegaly of the "expanded" congenital rubella syndrome.

Laboratory Studies

There are a wide number of laboratory studies available to assay the immune system. Certain of the tests are regularly done only in centers with a particular interest in children with immune defects, but many others are easily accomplished outside of such specialized settings.

A white blood cell count and morphologic examination of the peripheral blood can provide detailed information on the numerical adequacy of the cells necessary for immune responsiveness. The absolute cell count, derived by multiplying the total number of white cells by the percentage of the specific cell type involved, is a more accurate measure of cellular adequacy than is a simple white cell differential. Absolute neutrophil counts below 1800 cells per cu mm or absolute lymphocyte counts below 1500 cells per cu mm are abnormal and may indicate significant cellular deficiency.

In certain patients with recurrent infections, particularly those with such problems as recurring stomatitis, the absolute neutrophil count may be low only at certain regular intervals. Should a cyclic neutropenia be suspected, several neutrophil counts obtained over a four to six week period are useful, as the typical interval between episodes of neutropenia is usually about 21 days. Finally, an occasional patient may have a defect in granulocyte function even though these cells are adequate in number. These syndromes associated with a quantitative granulocyte defect usually require specialized laboratory tests for diagnosis. However, at least one of them, the Chediak-Higashi syndrome, can be diagnosed by the presence of characteristic giant granules contained in all leukocyte varieties, but especially in the neutrophils.

TABLE 2.—*Disorders of the Host Response to Infection—Clinical*

<i>Disorder</i>	<i>Genetics</i>	<i>Clinical Presentation</i>	<i>Defect</i>	<i>Screening Test</i>
Bruton-type hypogammaglobulinemia	X-linked	Pyogenic infections usually after the first 6-months of life; rheumatoid like arthritis	Absent circulating antibodies	Schick test, Isohemagglutinins (either may be invalid in first 6-months of life)
Isolated IgA deficiency	?	Sinusitis; pulmonary, gastrointestinal infections	Absent secretory antibodies	Quantitative IgA
Thymic dysplasia	X-linked	Severe bacterial and viral infections early in life	Dysplastic thymus	Peripheral lymphocyte count, chest X-ray for thymic shadow
DiGeorge Syndrome	?	Severe bacterial and viral infections neonatal hypocalcemic tetany, cardiovascular and facial anomalies	Absent thymus and parathyroid glands	Same as above, serum calcium
"Swiss-type" Agammaglobulinemia	Autosomal recessive	Severe bacterial and viral infections early in life	? defective bonemarrow stem cell	Peripheral lymphocyte count, chest X-ray for thymic shadow
Wiskott-Aldrich Syndrome	X-linked	Eczema, thrombocytopenia, sinusitis, pulmonary infections	?	Absent isohemagglutinins, low platelet count
Chediak-Higashi Syndrome	Autosomal recessive	Partial albinism bacterial infections neurologic disorders, lymphoreticular malignancies	?	Giant granules in leukocytes
Chronic granulomatous disease	X-linked	Recurrent pyogenic infections with abscess and granuloma formation	Neutrophil killing defect	NBT test

In addition, red cell examination for Howell-Jolly bodies may be done to evaluate adequate splenic function. And, finally, one may note the thrombocytopenia seen in the Wiskott-Aldrich syndrome or the impressive eosinophilia or monocytosis seen at times with congenital hypogammaglobulinemia.

Radiology

Radiologic examination can provide important information in assessing children who may have an immunologic deficiency. Absence of lymphoid tissue as judged from a lateral x-ray film of the neck is typical of the syndrome of congenital hypogammaglobulinemia. The chest film may be valuable in assessing thymic size but care must be taken not to interpret the small thymic shadow of children with severe infection as evidence of a basic thymic defect.

The right-sided aortic arch and other cardio-

vascular anomalies of the DiGeorge syndrome may also be recognized on a plain film of the chest. In some clinics a barium swallow is added to identify the monilial esophagitis which often accompanies thymic dysplasia.

Most children with an immune deficit, though, are unlikely to demonstrate other congenital anomalies, although dwarfing has been recently noted in a few children with a severe generalized immunologic disorder.¹⁶

Specific Immunologic "Screening"

In children over one year of age, there are three rapid, easily performed tests which may quickly characterize the integrity of the serum and cellular immunologic factors. (See Table 2.) If the child has received DPT immunizations, one can perform a Schick test, using diphtheria toxoid. In the absence of antitoxoid antibodies, which are of the γ C type, an erythematous reac-

tion develops at the injection site, and the child is described as "Schick-positive." A Schick-negative child must, therefore, have functional circulating γ G antibodies.

The presence of functional γ M antibodies can be demonstrated by the presence of the natural isohemagglutinins anti-A and anti-B, a test which any blood bank can perform. If the child is type A, B or O, a titer of anti-A or anti-B of 1:8 or greater can be expected after 6 to 9 months of age. Obviously, if the child is type AB, this is not a useful test, since no isoantibodies are formed normally.

To test cellular immune responsiveness, intradermal skin tests with such commercial antigens as monilia or purified protein derivative (PPD), or with mumps virus vaccine which has been heated to 100°C for 30 minutes may be performed. Provided the child has had previous exposure to the test antigen, failure to respond is suggestive of a cellular immune deficiency.

If the child's history of exposure is uncertain, one may expose him to certain organic sensitizers, such as dinitro-chloro-benzene (DNCB). One initially applies a patch to the skin after moistening it with DNCB. A second patch moistened with DNCB and applied two weeks later should bring out a strong positive reaction in more than 95 percent of patients. Unresponsiveness, particularly after a second challenge, is very suggestive of a cellular immune deficiency.

Special Immunologic Tests

The most frequently mentioned test, and the test one might expect to turn to first in diagnosis of an immune deficiency state, is serum protein electrophoresis. This test has a venerable history, having been used by Col. Ogden Bruton in the diagnosis of his original patient with hypogammaglobulinemia in 1952. However, since that time misinterpretation of the results of this test has been responsible for many incorrect diagnoses and the misuse of massive amounts of gamma globulin. The reasons for these errors are twofold. Protein electrophoresis separates the serum proteins into four major classes, depending on their ability to move through an electric field. These include the serum albumin and three classes of globulins, alpha, beta and gamma. Although nearly all the gamma globulin fraction is composed of antibodies, some antibodies are also

found among the beta globulins. Thus a selective deficiency of beta globulin antibodies may not be detected by serum protein electrophoresis. Further, since this test only measures the total of a large group of antibodies, one may have a "normal" pattern with certain antibody types in excess, while others are seriously low. It cannot be overemphasized that protein electrophoresis, in general, is too inaccurate and insensitive a test on which to base an estimate of immunoglobulin levels in a diagnosis of immune disorders except in the rare child in whom the gamma globulin fraction is virtually absent.

A rapid, reliable test is available now to specifically quantitate IgG, IgM and IgA, the three major antibody classes present in human serum. Estimation of the amount of each type present is essential to accurate immunologic diagnosis. The test employs a gel diffusion technique in which the patient's serum is placed in a small hole cut into agar which already contains specific animal antibodies prepared to detect IgG, IgM or IgA proteins. As the patient's serum diffuses through the specific antibody in the agar, a precipitate is formed. The size of the precipitate ring is a measure of the amount of the specific immunoglobulin present in the serum sample. Extremely small amounts of the three antibody groups can be measured in this way, and specific deficiencies in any one of the groups are easily detected. However, in interpreting the results of this test it is essential to know the normal immunoglobulin levels for the patient's age group. Many diagnoses of "hypogammaglobulinemic" have been due to the mistaken comparison of children's immunoglobulin levels with adult standards. When this test is carefully performed, and age-appropriate standards are used, it is the single most valuable test we have to diagnose a quantitative deficiency of circulating antibodies.

At this point in the work-up, one knows in a general way whether his patient has functioning antibodies of two of the three major classes, whether the three major immunoglobulin groups are quantitatively sufficient, whether there are numerically adequate circulating neutrophils and lymphocytes, and whether the child can muster a delayed-hypersensitivity response to some common antigens. If there is a good reason to suspect that some, or all, of these functions are impaired, referral to a center where more detailed, special-

ized examinations are available is indicated. Studies which might then be carried out would include the following:

1. Measurement of specific antibody response to such antigens as diphtheria or tetanus toxoid after immunization with these materials.

2. Examination of the architecture of lymph nodes draining an area in which an antigen has been injected. Failure of the node to show an active cellular response, with numerous primary and secondary follicles, may be a major aid in identifying several types of immunologic disorders.

3. Investigation of defects in the cellular or delayed hypersensitivity response can be carried out by a number of sophisticated tests. In one, the patient's lymphocytes are exposed in tissue culture to such stimuli as the mitogenic factor known as phytohemagglutinin (PHA). Normal lymphocytes undergo a dramatic transformation in the presence of PHA, becoming large blastlike cells undergoing mitosis in about 72 to 96 hours and incorporating radioactive thymidine into their DNA. However, persons with defective delayed immunity often have lymphocytes unresponsive to PHA. This PHA test has much replaced the older technique of exposing the patient to a small graft of foreign skin and then observing his ability to accomplish a graft rejection. Skin grafting is infrequently performed today because of the possibility of sensitization of the recipient to foreign tissue antigens which might coincidentally be shared by immunologically active grafts later given to the patient as a mode of therapy.

4. Finally, there are certain areas outside the province of classical immunology in which techniques are available to assess a patient's non-specific ability to cope with infection. These areas include an assessment of the phagocytic ability of the neutrophils and a study of the complement system. Laboratories capable of carrying out full studies of the adequacy of the complement system are located in only a few hospitals, but increasingly they are making their services available for the evaluation of any patient in whom a disorder of the complement system is suspected. An inability of the neutrophils to kill bacteria or fungi after ingesting them is characteristic of chronic granulomatous disease and certain of the chronic candidiasis syndromes. A rapid, easily performed test has recently been

developed which can detect not only the defects of the patient's cells, but also those unaffected persons who are genetic carriers of these disorders. This test of phagocytosis depends on the fact that once neutrophils engulf bacteria, they undergo several bursts of metabolic activity. Some of these stimulated metabolic pathways are available to carry out oxidation-reduction reactions, presumably as a way the neutrophil disposes of its bacterial meal. If one exposes the yellow dye reduced nitroblue tetrazolium (NBT) to these activated neutrophils, it will be converted to its deep blue oxidized form, "formazan." A normal NBT test, then, ends with a number of the neutrophils filled with large purple formazan granules, easily seen in the microscope. An absence of these granules may provide an important clue to the diagnosis of certain congenital defects of the response to infection.

As the host response to infection is further studied, newer ways of judging normal and abnormal function will be developed, and newer ways of restoring abnormal functions to normal are certain to follow.

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Cervical Mediastinal Exploration and Open Lung Biopsy

G. ROBERT MASON, M.D., *Stanford*

EITHER OPEN LUNG BIOPSY or cervical mediastinal exploration based on the x-ray findings was carried out in 50 consecutive cases of indeterminate lung lesions, in which standard non-surgical diagnostic techniques of sputum culture, serology, cytology and skin tests were not definitive. A definitive diagnosis was obtained in 97 percent of the lung biopsies and 80 percent of the mediastinal biopsies. There were no deaths from either procedure. The only complications were superficial wound infection after lung biopsy in two cases.

In the differential diagnosis of pulmonary disease, histologic examination of pulmonary or nodal tissue is often the only satisfactory method of defining the disease entity. Procedures short of formal thoracotomy include cervical mediastinal exploration and open lung biopsy. A series of 50 cases in which these procedures were done was reviewed in an attempt to ascertain certain general principles related to indications for them.

Material

The patients had all been admitted to Stanford University Hospitals and represent consecutive cases on the author's service. Presenting signs and symptoms varied, from the asymptomatic density found on annual x-ray film of the chest to those of acute respiratory disease. For purposes of discussion, the 50 cases will be divided according to the findings on chest x-ray films. In 23 cases, the presenting radiologic abnormality was a pulmonary infiltrate (Table 1). After appropriate work-up, including cultures and skin tests, lung biopsy by Klassen's technique¹ was

carried out in 22 cases, and in 21 it resulted in positive diagnosis. One patient was found by lung biopsy to have pneumonitis (non-specific) but Hodgkin's disease was diagnosed by bone marrow biopsy. One patient admitted because of lung infiltrate, was observed on mediastinal tomography to have a single lymph node above the azygous vein. On mediastinal exploration, biopsy of this node by Carlen's technique² showed sarcoidosis.

Nineteen patients had peripheral lung density on chest x-ray films (Table 2). Six of these patients had no mediastinal abnormalities on tomography but on biopsy of the lung as described above three were found to have metastatic malignant lesions, two had granulomas and one a pulmonary infarct. The remaining 13 patients had mediastinal densities in addition to the peripheral lesion. Two of these patients were found to have Hodgkin's disease on lung biopsy. In 11 cases a collar incision (Carlen's) was made and biopsy specimens were taken, in most cases concomitantly with bronchoscopy. In seven of these cases, a diagnosis was made from the biopsy—carcinoma of the lung in five, tuberculosis in one and sarcoïd tumor in one. The diagnosis in the other four cases was carcinoma of the lung, but was made from bronchial washings in two cases, from rib biopsy in one case and at thoracotomy in the remaining case. In this last case diagnosis should have been at the original mediastinal exploration, as positive mediastinal nodes were present.

Eight patients presented with mediastinal masses only (Table 3). All had mediastinal exploration. In this group, biopsy showed sarcoid in two cases, lymphoma in one, Hodgkin's disease in one, thymoma in one and metastatic cervical carcinoma in one. Two patients were found on careful exploration to have dilated and

From the Department of Surgery, Stanford University School of Medicine.

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Reprint requests to: G. R. Mason, M.D., Department of Surgery, Stanford University School of Medicine, Stanford, Ca. 94305.

TABLE 1.—Nature of Pulmonary Infiltrate in 23 Cases

	<i>No. of Cases</i>
Diffuse interstitial fibrosis	3
Periarteritis	3
Necrotizing bronchitis	3
Neoplasm	2
Fungus (non-specific caseating granuloma)	2
Hodgkin's disease	2
Non-specific fibrosing lesions	2
Sarcoid tumor	2
Silicosis	1
Loeffler's syndrome	1
Hemosiderosis	1
Henoch-Schonlein	1

TABLE 2.—Nature of Lesion in 19 Patients with Lung Mass

	<i>No. of Cases</i>
Lung Mass plus Mediastinal Mass (11 Cases)	
Neoplasm	9
Tuberculosis	1
Sarcoid	1
Lung Mass only (8 Cases)	
Neoplasm (metastatic)	3
Hodgkin's	2
Granuloma	2
Infarct	1

tortuous subclavian arteries which corresponded in configuration to the mediastinal masses. No biopsy specimens were taken.

Accuracy in diagnosis was 29 of 30 in the lung biopsy group and 16 of 20 in the mediastinal biopsy group. There were no complications in the mediastinal biopsy series and two minor wound infections in the lung biopsy series.

Discussion

Routine diagnostic procedures for a patient presenting with a pulmonary infiltrate or mass include skin tests, culture and cytologic examination of sputum, and a search for older films of the chest. In some cases, chest tomography or radiologic study of other organs may be indicated. These studies plus a good history often can separate the infectious processes from the neoplasms and connective tissue disorders, allowing treatment to be initiated. (One of the series of patients reported here had tuberculosis diagnosed only by mediastinal node biopsy after multiple negative cultures of sputum.) In the remaining cases, a tissue diagnosis is usually required as the next step. Even if an ancillary intra-abdominal neoplasm is suspected or con-

TABLE 3.—Nature of Lesion Presenting as Mediastinal Mass (8 Cases)

	<i>No. of Cases</i>
Sarcoid	2
Dilated subclavian	2
Lymphoma	1
Hodgkin's disease	1
Thymoma	1
Metastatic carcinoma	1

firmed, the nature of the thoracic lesion will determine much of future therapy. Relatively minor surgical techniques available at this point include needle aspiration biopsy, bronchoscopy, pre-scalene fat pad biopsy, open lung biopsy or mediastinal exploration. Needle aspiration biopsy has been useful particularly in peripheral neoplasms where a cytologic diagnosis may be achieved. Aspiration biopsy of inflammatory tissue or positive bacterial culture from such tissue does not eliminate the possibility of neoplasm and requires further investigation. Our radiologists have been hesitant to biopsy hilar or mediastinal lesions or diffuse infiltrates, feeling that the complications outweigh the likelihood of diagnosis. Complication rates for needle aspiration may vary from 11.6 percent³ to 45 percent.⁴ In the largest reported series of cases of needle biopsies the diagnosis was established in approximately 50 percent of 623 cases.³ In the series of cases reported here, five patients had satisfactory criteria for needle biopsy. One patient had this procedure performed with negative results.

Pre-scalene node biopsy has been reported to be positive in a high proportion of cases in which nodes are palpable, but probably in only about 20 percent of cases when no nodes are palpable.⁵ Lawton and Brintnall described 36 cases in which scalene node biopsy and mediastinoscopy⁶ were done at the same time. In their series, scalene biopsy was not positive in any case in which mediastinal nodes were negative. Twenty-five percent of mediastinal biopsies and 12 percent of scalene biopsies were positive. Considering reports of 9 percent⁵ complications from pre-scalene node biopsy as opposed to reports of 0 to 3 percent for mediastinoscopy,^{2,7,8} the procedure of choice between the two would seem clearly to be mediastinoscopy. There were no complications and positive results in 80 percent of the 20 mediastinal biopsies reported herein.

In 15 of the 50 cases presented here, the final diagnosis was neoplasm—metastatic in four cases. Many thoracic surgeons believe that the presence of mediastinal nodes does not rule out the possibility of resection of the lesion. However, a recent survey of the literature indicates that exclusion of patients with positive mediastinal nodes from thoracotomy raises resectability rates from a low of 50 percent to as high as 95 percent. On the other hand, in a large series of patients reported by Jepson, only 1 percent of patients with mediastinal metastasis were alive at three years whether thoracotomy was done or not.¹⁰ During the five years 1966-1970 at Stanford University Hospital, there were 66 lobectomies, 23 pneumonectomies and 138 formal thoracotomies without resection. This latter group could have been considerably reduced by utilization of cervical mediastinal exploration or lung biopsy.

Open lung biopsy has been recommended by Siltzbach for diffuse chronic pulmonary disease such as sarcoidosis, Hamman-Rich disease, honeycomb lung, histiocytosis, pneumoconiosis and berylliosis.¹¹ Complication rates in a large collected series of cases that included subcutaneous emphysema, pneumothorax, hemothorax and atelectasis were said to be "minimal."¹² On the other hand, more deaths are noted following lung biopsy than the other procedures described here, ranging up to 18 percent.¹³ It should be noted, however, that some of these patients were severely ill at the time of biopsy and that the procedure was done as a last effort to find a treatable disease. Whether or not the procedure hastened the death of these patients is unknown.

Our experience with lung biopsy has led us to make recommendations similar to those made by Wolfe and Cole.¹⁴ Various acute and chronic pulmonary infections have been included in our series, as well as neoplasms of primary and secondary nature, systemic diseases such as periarthritis and circulatory problems such as hem siderosis and infarct. Because of reports of high incidence (80 to 100 percent) of positive mediastinal nodes in sarcoidosis,⁸ we did mediastinal biopsy rather than open lung biopsy in most of these cases. Tomography of the mediastinum is helpful in determining the location of adenopathy precisely.

With the increasing costs of hospital care, greater attention has been focused on bed utilization in this country. For the patient who is not

acutely ill with a pulmonary disorder, many of the routine diagnostic tests such as sputum culture and cytology, pulmonary function tests, skin testing and radiologic studies may be done on an out-patient basis. Once the decision has been made to admit the patient, definitive surgical procedures may be scheduled without delay. Mediastinal biopsy under general anesthesia through a cervical incision is recommended for any lesion which appears to have a mediastinal component, for suspected sarcoid, or when carcinoma is suspected and operability must be determined. Customarily, as others have recommended,¹⁵ we have combined this procedure with bronchoscopy and have obtained frozen section pathologic diagnosis with the object of proceeding directly to formal thoracotomy if this seems indicated. In general, however, the preliminary procedures have obviated thoracotomy. In these cases, the patient is usually discharged the next day to be given radiologic or other appropriate therapy.

Diffuse or isolated pulmonary infiltrates in both the acutely and chronically ill and isolated peripheral pulmonary nodules appear to be the most suitable for open lung biopsy. This procedure may be done safely under local or general anesthesia. Although a slightly greater morbidity is apparent after lung biopsy, most patients may be started on appropriate therapy immediately and those not requiring therapy may be discharged in two to three days.

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Medical Progress

Australia Antigen and the Revolution In Hepatology

G. L. GITNICK, M.D., *Los Angeles*

AUSTRALIA ANTIGEN OR HEPATITIS associated antigen (HAA) was first detected in the serum of an Australian aborigine by using as an antiserum a precipitating antibody which developed in hemophilia patients who had received multiple transfusions.^{1,2} Since that time it has been shown that this antigen is a particle intimately associated with, or a causative agent of, viral hepatitis.^{3,4} The steps leading to this determination represent a fascinating saga of medical and historical serendipity.

In 1963 Dr. B. S. Blumberg and his colleagues were in the midst of a systematic study exploring inherited variations in serum proteins. This was part of an extensive study of inherited and acquired antigens to which hemophilia patients may have developed antibodies following repeated transfusions.¹ During these studies an unusual antibody was found in the serum of a patient with hemophilia who had received many transfusions. In the initial experiments the antibody was found to react with the serum of an Australian aborigine but not with other sera in the panel. It was therefore called Australia Antigen (abbreviated Au(1)). The antigen was present in only 0.1 percent of the general United States population,⁵ but was detected in the blood of 8 of 70 patients with leukemia.^{3,6} Subsequently HAA was found in 28 percent of 310 patients with Down's syndrome who were in insti-

tutions but was rarely present among patients with Down's syndrome living out of institutions.^{3,7} Equally confusing was the finding of HAA in 5 percent of apparently normal people living in several Asian and oceanic countries. This led to studies which suggested Mendelian inheritance.^{8,9} The antigen was also found in seven of 38 patients with acute granulocytic leukemia and four of 30 patients with chronic lymphocytic leukemia. Many of these patients were subsequently found to have received transfusions and to have liver disease.³

Further studies revealed the antigen to be associated with long incubation period or post-transfusion hepatitis. Initial studies showed HAA to be detected in up to 58 percent of such patients, as determined by immunodiffusion studies.^{3,10} The association of HAA with acute hepatitis was quickly confirmed by Okochi and Murakami.⁶ Early studies were done primarily using the relatively insensitive Ouchterlony immunodiffusion technique. However, in 1969 two groups independently described highly sensitive complement fixation assays for HAA.^{11,12} This led to studies revealing that by testing serial sera, HAA could be detected in up to 98 percent of 130 patients with post-transfusion hepatitis.¹¹ These studies firmly established the association of HAA with acute hepatitis.

After partial purification by sucrose density gradient ultracentrifugation, HAA was examined under the electronmicroscope by Bayer.¹³ HAA was found to be composed of 200-Angstrom

From the Division of Gastroenterology, Department of Medicine, University of California, Los Angeles, Center for the Health Sciences.

Reprint requests to: G. L. Gitnick, M.D., University of California, Los Angeles, Center for the Health Sciences, 10833 Le Conte Avenue, Los Angeles, Ca. 90024.

particles with sub-units 30 Angstroms in diameter. Immunofluorescent studies consistently demonstrated HAA in and around the nuclei of liver cells of patients with viral hepatitis and HAA in their blood.¹⁴ The antigen was not demonstrable in other forms of acute liver disease, either by immunofluorescence studies of liver preparations or by evaluation of the blood of patients, using immunodiffusion techniques. Prince, using a similar method, demonstrated the presence of an antigen in the sera of patients with post-transfusion hepatitis but not in the sera of patients with infectious hepatitis. He designated this antigen as "SH" antigen.¹⁵ Subsequent studies have shown that SH antigen forms a band of identity with HAA.¹⁶ Accordingly, hepatitis associated antigen or HAA, Australia antigen or Au(1) and SH antigen, are now thought to be identical determinants. Because of the association of Australia Antigen with acute hepatitis, evidence that it can be transmitted by transfusion, together with the electronmicroscopic appearance and its demonstration by immunofluorescence studies in or on the nuclei of liver cells, it has been suggested that HAA may indeed be a virus which could be an etiologic agent of hepatitis.¹⁰

In 1969 Wright and his colleagues¹⁷ and my colleagues and I¹⁸ independently demonstrated the presence of HAA in the sera of patients with chronic active liver disease. These studies demonstrated that the antigen may persist for weeks, months or years among patients with chronic liver disease even though the liver is cirrhotic. Blumberg and his colleagues had already demonstrated the presence of the antigen among patients with Down's syndrome and anicteric chronic liver disease.³ It has accordingly been suggested that HAA may be acting as a "slow" virus. London and his colleagues suggested that these findings, together with the appearance of HAA among patients with Down's syndrome, leukemia and lepromatous leprosy, may indicate an association with some form of immunologic deficiency.¹⁹

Recently Australia antigen subtypes have been defined^{20,21,22} and the possible clinical implications of such subtypes have been explored. In addition to the initial association of HAA with acute hepatitis and the subsequent demonstration of HAA in chronic active hepatitis and post-necrotic cirrhosis, further studies have demon-

strated the variable presence of HAA among patients with primary biliary cirrhosis, neonatal hepatitis,^{23,24,25,26} hepatoma,²⁷ and periarteritis nodosum.^{28,29} Finally, circulating antigen-antibody complexes have been demonstrated among patients whose HAA complement fixation tests were anti-complimentary. Accordingly, therapeutic and prognostic significance has been attached to the presence of an anti-complimentary or "AC" HAA assay.³⁰

Assay Systems

Several valuable tests are now available for the detection of HAA. When antigen is present in high concentrations most of the available assay systems are capable of detecting it. However, antigen that is present in low concentrations may be detected only in the more sensitive systems. The Ouchterlony agar gel diffusion system was the first assay developed for the detection of HAA.³¹ This system usually requires at least 24 hours before results are available. Current data suggest that this is the least sensitive assay for the detection of HAA.³² Counter-electrophoresis is one of the most widely used assay systems for screening for HAA. This system offers the advantages of being rapid, relatively inexpensive and easy to perform, and it is more sensitive than standard immunodiffusion systems. However, this assay system lacks the sensitivity of the following tests. Complement fixation is a highly sensitive means of detecting HAA.^{11,12} The standard test requires 24 hours. Variations of the test may be performed within three hours. This assay is relatively inexpensive and is sensitive, but requires a skilled technician and a reliable control system. Recently an automated complement fixation assay was described.³² This system, which requires only 45 minutes for the performance of 60 tests on a single channel of an autoanalyser, may provide a rapid automated inexpensive means of screening in large blood centers. The hemagglutination inhibition assay is thought to be a very sensitive, relatively rapid and inexpensive test for the detection of HAA.³³ This is a new test and has not been thoroughly evaluated. Initial data suggest that this may be a sensitive and reliable assay system which will yield results within a short period and can easily be performed. The reagents for this system currently are relatively expensive. This assay system may lend itself to automated procedures.

The most sensitive assay for HAA is the radioimmunoassay.³⁴ This assay takes several days to perform, is technically difficult and requires highly trained personnel for performance and interpretation. Currently this assay system does not lend itself to rapid, large-scale screening procedures.

Physical and Chemical Properties

Electronmicroscopic studies of partially purified antigen preparations have revealed virus-like particles 200 Angstroms in diameter.¹³ These particles may be tubular or spherical in shape and may contain a dense core. Most particles appear empty. The surface consists of symmetrical polyhedral sub-units 30 Angstroms in diameter. These particles may be agglutinated by specific antibodies. Other studies have revealed the occasional presence of large oval particles 200 m μ in diameter. Recently studies have demonstrated small amounts of RNA in purified antigen preparations. The characteristics previously described are entirely consistent with those of a small virus. However, Koch's postulates have not been fulfilled. Krugman has recently shown that the infectious moiety of HAA may be inactivated by heat, and in this manner he has produced an experimental hepatitis vaccine.³¹

Acute Hepatitis

Studies by several groups, including the important contributions of Blumberg,³ Prince,¹⁵ Giles,³⁵ and Krugman,^{36,37} have established a definite association between HAA and long incubation period or serum hepatitis. In one series HAA was detected in 97 percent of 40 cases of post-transfusion hepatitis but was not detected in 41 consecutive cases of short incubation period or infectious hepatitis.³⁷ With the development of the HAA complement fixation assay, Shulman was able to demonstrate that HAA could be detected in at least one of four serial sera of 98 percent of patients with documented post-transfusion hepatitis.¹¹ Some investigators have associated the antigen with short incubation period hepatitis or infectious hepatitis. These findings have not been uniformly observed. It has been suggested that the infrequent association of HAA with infectious hepatitis may reflect the fecal-oral transmission of HAA hepatitis. Among the many im-

portant contributions made by Krugman to our understanding of hepatitis was the demonstration that the agent of long incubation period hepatitis, though usually transmitted through blood products, could also be transmitted by the oral route.³⁶ The test for HAA is a helpful aid in differentiating between infectious and serum hepatitis, or between serum and drug-induced hepatitis. A negative HAA test does not rule out the presence of long incubation period hepatitis because the duration of antigenemia may be transient. The antigen may be present for as short a period as two or three days, or as long a period as 21 days. It may not be detectable shortly after the onset of jaundice and it may rapidly disappear after the transaminase has reached its peak.

During past years it has been reported that in the United States the annual rate of post-transfusion hepatitis amounts to approximately 30,000 cases. Furthermore, it has been estimated that there may be up to 3,000 deaths a year as a direct result of post-transfusion hepatitis.³⁸ Most blood banking centers have now instituted routine testing of blood and blood products for HAA. In some centers the frequency of post-transfusion hepatitis has been reduced by 25 percent or more, but nowhere has it been eliminated. A number of techniques are available for HAA testing. It is unfortunate that those which lend themselves most easily to large scale screening procedures are the least sensitive assays. The more sensitive assays, such as the radioimmunoassay, the hemagglutination inhibition test and the complement fixation assay, require time, money and technical skill. The application of automated procedures to these assay systems may provide rapid, inexpensive and highly sensitive assays through routine use in large blood banks.³²

Initial studies reported by Krugman have suggested that gamma globulin made from plasma containing antibody to HAA may effectively reduce the risk of post-transfusion hepatitis.³¹ Thus far only small scale studies have been recorded, yet the data is encouraging. In contrast, gamma globulin lacking antibody to HAA seems ineffective. Gocke³⁹ administered plasma containing antibody to Australia antigen to a small group of patients with fulminant hepatitis and reported subsequent amelioration of disease. A controlled prospective study of the potential therapeutic

value of HAA in the treatment of fulminant hepatitis is under way. A patient so treated by our group did not survive.

An experimental hepatitis vaccine was recently prepared by Krugman.³¹ The serum, containing HAA, was heat-inactivated and was administered to a small group of children. When challenged with hepatitis inoculations the children who received the heat-inactivated vaccine were apparently immune, whereas hepatitis developed in children not so protected. These studies suggest that a hepatitis vaccine could be feasible. However, it is unlikely that a heat-inactivated vaccine prepared from human serum would lend itself to the extensive safety precautions required for large scale vaccine production. This important work, however, did demonstrate that inactivated HAA may confer protection. It is hoped that this pioneer work will lead to the development of vaccines produced from HAA cultivated in tissue culture and subsequently either attenuated to produce a live attenuated vaccine or inactivated by other methods of inactivation.

Chronic Active Liver Disease

At the time that the presence and persistence of HAA in the sera of some patients with chronic liver disease was demonstrated,^{17,18} it was postulated that HAA may be acting as a slow or latent virus. Subsequent studies have confirmed and extended these findings. HAA has been detected in between 10 and 50 percent of patients with chronic active liver disease. During the course of this illness the antigen may come and go, perhaps reflecting variable concentrations of antigen or a varying sensitivity of our HAA assays. HAA may be present even though the liver is cirrhotic.¹⁸ In some instances circulating antigen-antibody complexes have been demonstrated⁴⁰ and it has been suggested that these complexes may be important in the progression of this disease. Such complexes may be demonstrated by the detection of anticomplementary (AC) HAA complement fixation assays. Alternatively, antigen and antibody may be demonstrated to co-exist in the same serum by application of either the radioimmunoassay or the hemagglutination inhibition assay. Each of these approaches has successfully demonstrated the presence of HAA complexes in some patients with chronic active liver disease.⁴¹ Recent studies by our group have demonstrated that HAA or antigen-antibody com-

plexes may be detected in more than 50 percent of patients with chronic active liver disease.³⁰ Patients found to have anticomplementary assays tend to have a poorer prognosis than do those who do not. Moreover, patients with circulating immune complexes or anticomplementary assays show the most dramatic response to treatment with prednisone. Unfortunately a large series in which some patients with chronic HAA antigenemia are treated with prednisone and others with placebo has not yet been reported. Our series is not large enough to yield data of statistical significance and hence the question of whether chronic antigenemia lends itself to treatment with prednisone remains unanswered.

Postnecrotic Cirrhosis

Acute hepatitis sometimes progresses to chronic active hepatitis and subsequently to post-hepatic or postnecrotic cirrhosis.⁴² In each of these entities, HAA which first developed during acute hepatitis may persist. Thus the presence of HAA among patients with postnecrotic cirrhosis is now well documented.¹⁸ The pathogenic implications of this finding and the associated therapeutic possibilities remain unexplored. The role of HAA in the progression through this spectrum of liver disease is undetermined.

"Persistent Hepatitis," "Unresolved Hepatitis" and "Hippy Hepatitis"

The sequelae of acute hepatitis are numerous. One of these is a benign lesion characterized by a heavy inflammatory infiltrate in portal tracts but not associated with hepatocellular necrosis or lobular destruction. This pathologic lesion has been designated "persistent hepatitis."⁴³ The same lesion may be found as a result of a number of causes, only one of which is acute hepatitis. Patients with this lesion usually are relatively asymptomatic but may have persistent elevations in transaminase values, and a significant number of such patients may have chronic HAA antigenemia. The natural history of this illness is usually a spontaneous resolution after weeks, months or years. It is not thought to progress to cirrhosis.⁴⁴ In contrast, "unresolved hepatitis" is characterized by inflammatory infiltration and variable degrees of hepatocellular necrosis and may be associated with clinical symptoms. It is frequently associated with chronic Australia an-

tigenemia. The natural course of this lesion is not well delineated. Finally, the term "hippy hepatitis"⁴⁵ has been applied to chronic liver disease initially thought to be related to the administration of intravenous narcotics. Some cases of this chronic form of liver disease have been found to be associated with Australia antigenemia. Indeed, antigen titers have been found to be unusually high, perhaps because of frequent and heavy exposure.

Neonatal Hepatitis

The role of HAA in maternal and neonatal hepatitis has been extensively investigated. Keyes^{25,26} and other members of our group evaluated sera from mothers and infants participating in a collaborative perinatal study encompassing 60,000 pregnancies. Populations studied included mothers with hepatitis during pregnancy, mothers delivering stillborn infants and mothers having repeated abortions. Also studied was cord blood from mothers with hepatitis during pregnancy and from newborns with hyperbilirubinemia, Down's syndrome or elevated immunoglobulin M levels. Of 22 mothers with hepatitis during pregnancy, two were positive for HAA (9.1 percent). HAA may have been acquired by the fetus during intrauterine gestation, since the cord blood from one of the two mothers was also positive. This was the first demonstration of HAA in cord blood. This finding supports the possibility that HAA may be transmitted to the fetus via the placental circulation. In contrast, other investigators had previously suggested that HAA may also be contracted by the fetus from swallowing amniotic fluid *in utero*. HAA was found in one of 30 (3.3 percent) mothers who had repeated stillbirths, in one of 27 (3.7 percent) with repeated abortions, and also in the cord blood of two of 123 mothers (1.6 percent) with elevated igM levels.

Schweitzer²³ reported the occurrence of HAA in some infants whose mothers had HAA-positive hepatitis. Keyes²⁶ evaluated 414 pairs of maternal and cord blood specimens from a county hospital population, using the HAA complement fixation and immunodiffusion techniques. Four maternal blood specimens were found to be positive (1 percent). One infant whose mother had HAA at delivery became positive at one month of age. This infant's circulating HAA has per-

sisted throughout the early months of life. Currently the significance of chronic HAA antigenemia in infants is uncertain.

Primary Biliary Cirrhosis and Primary Liver Cell Carcinoma

Two lines of evidence have implicated HAA in the pathogenesis of primary biliary cirrhosis. Electronmicroscopic studies originally revealed antigen-like particles in the sera of a few patients with the disease. Subsequently, highly sensitive assays also detected the antigen in occasional patients with this illness. Recently, a prospective double-blind controlled trial of treatment among patients with chronic active hepatitis yielded other important data which may cast light on the pathogenesis of some cases of primary biliary cirrhosis.⁴² Sixty-five patients with chronic active hepatitis were followed prospectively. All had presented with typical clinical, biochemical and histologic features of chronic active hepatitis. Serial biopsy studies were done, and in seven of the patients features characteristic of primary biliary cirrhosis subsequently developed. Of these seven, three were found to harbor HAA. Hence it is suggested that a few patients with chronic active hepatitis may progress to primary biliary cirrhosis, and that HAA, acting as a "slow" virus, may persist in such instances. Thus far most patients having primary biliary cirrhosis do not appear to be HAA-positive, nor do they necessarily pass through a chronic active hepatitis stage. Another unusual outcome of HAA-positive liver disease is the development of primary liver cell carcinoma or hepatoma. Denison recently demonstrated the persistence of HAA in some patients with familial primary liver cell carcinoma.²⁷ Sherlock⁴⁶ had previously observed HAA to be present in some patients with hepatoma.

Polyarteritis, Glomerulonephritis and Arthritis

It has recently been demonstrated that HAA may be detected in some illnesses not ostensibly related to liver disease. Gocke et al²⁸ evaluated 11 patients with polyarteritis manifested by arthralgia, urticaria, fever, hypertension, hematuria, azotemia and eosinophilia. Four of these 11 patients had circulating serum HAA associated with mild hepatitis. Circulating antigen-antibody

complexes were demonstrated in three of the four patients. Further studies revealed the presence of iGM, HAA and the C³ component of complement in the walls of a skeletal muscle artery. Evaluation of these patients revealed that most had previously experienced an episode of HAA-positive hepatitis. In another instance, antigen-antibody complexes were demonstrated to be deposited within the glomeruli of the kidneys of a patient with HAA-positive chronic hepatitis and glomerulonephritis.⁴⁷ In the latter instance it was postulated that HAA or antigen-antibody complexes may be important in the pathogenesis of the renal lesion. Arthritis simulating rheumatoid arthritis, but lacking rheumatoid factor, may accompany acute or chronic hepatitis. Alpert evaluated nine cases of hepatitis associated with arthritis.⁴⁸ Four of the patients had urticaria and four had skin rashes. All patients had HAA in their serum. Serum complement levels or individual complement components were low. Alpert suggested that this may reflect the presence of immune complex disease. Thus emerging evidence suggests that HAA, or antigen-antibody complexes related to HAA, may be important in the pathogenesis of diseases involving organ systems other than the liver.

The Future

As described above, initial data suggests that basic research leading to the cultivation of HAA and the inactivation of HAA may eventually yield an effective and safe hepatitis vaccine. Extensive efforts will be required to cultivate, characterize, attenuate or inactivate the hepatitis virus before a hepatitis vaccine is a reality. Initial data also suggests that HAA detection may have therapeutic and prognostic significance. The detection of HAA circulating immune complexes among patients with chronic active liver disease seems to be an indicator of the need for treatment with steroids.

The significance of HAA in the serum of patients with chronic active liver disease in the absence of immune complexes has yet to be evaluated. Recent data suggests that there are at least four subtypes of HAA. The possible pathogenetic and prognostic significance of HAA subtypes will require extensive research. Early data supports the value of antibody to HAA in the prophylaxis of long incubation period hepatitis, and other data suggests that HAA antibody may

have an important therapeutic role in the treatment of fulminant hepatitis. These data will require confirmation and extension.

A Unifying Concept

HAA has now been detected in a variety of illnesses. Firm data establishing the role of HAA in the majority of these illnesses is not available. Circumstantial evidence would suggest that the sequelae of HAA-positive, acute hepatitis include a spectrum of liver disease. Thus the majority of cases resolve without after-effects. A few patients, however, may develop HAA-positive persistent hepatitis, unresolved hepatitis, fulminant, fatal hepatitis, or chronic active hepatitis. Of those in whom chronic active hepatitis develops some may progress to HAA-positive postnecrotic cirrhosis, and hepatoma may develop in a few. Other patients may progress through a chronic active phase into a phase characteristic of primary biliary cirrhosis. Occasional patients with circulating HAA may develop immune complexes which deposit outside of the liver. In the blood vessels polyarteritis may develop and in the kidney glomerulonephritis may be seen. This concept is suggested only as a postulate, for firm data supporting these pathogenetic routes is lacking. Blumberg's initial discovery of HAA has truly led to a revolution in hepatology. Newer concepts of the pathogenesis of liver disease and newer approaches to the treatment of liver disease have become an important part of this revolution.

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RECURRING PNEUMONIA IN INFANTS?—THINK OF OBSTRUCTION

What should you be on the look-out for when you see persistent or recurring pneumonias in the infant or young child?

In the broadest terms it would be bronchial obstruction. The natural tendency is to think of foreign body obstruction first which actually, despite its importance, is not very common. You think of compression of the bronchus due to lymphadenopathy, not as common now as formerly when there was a childhood tuberculosis. The most common cause is none of these dramatic things, but just the simple retained secretions following acute lower respiratory infections. Part of the lung becomes poorly aerated, and secretions are so tenacious they are not coughed up; spontaneous mechanisms just don't seem to take care of the situation in many cases. This is recognized, of course, only when bronchoscopy is done. I think we do have to think of the obvious mechanical causes of obstruction, but not disregard the simpler and more frequent matter of retained secretions following acute respiratory infection.

—CHARLES M. NORRIS, M.D., Philadelphia
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Specialty Conference

Alveolar Hypoventilation Caused by "Vera's Disease"—A New Disorder?

(Thoracic and Abdominal Muscle Contracture)

Moderator: EUGENE D. ROBIN, M.D.

Participants: NORMAN J. LEWISTON, M.D., JAMES THEODORE, M.D.,
JEFFREY BALFUS, M.D., MARK YZUEL, B.S., LARRY SIMON, M.D.,
FRED ELDRIDGE, M.D., GRANT FLETCHER, M.D.,
GEORGE FISHER, M.D., AND MARSHA ARMSTRONG, M.D.

*Pulmonary Rounds of the Respiratory Division, Stanford University School of
Medicine—Edited by Drs. Norman J. Lewiston and Eugene D. Robin*

EUGENE D. ROBIN, M.D.:* Alveolar hypoventilation occurring in patients with structurally normal lungs and heart is a problem of great clinical interest. In the past two weeks we have had an opportunity to see an unusual example of this variety of respiratory disease. Pathophysiologically this form of alveolar hypoventilation is relatively simple but the pathogenesis and etiologic delineation of the primary disease are unknown and indeed the primary disease may not have been previously described. We thought we would take this opportunity to discuss both the alveolar hypoventilation with a structurally normal respiratory apparatus and the differential diagnosis in a most unusual patient.

*Professor of Medicine and Physiology; Acting Chairman, Department of Medicine.

Reprint requests to: E. D. Robin, M.D., Department of Medicine, Stanford University School of Medicine, Stanford, Ca. 94305.

Case Presentation

NORMAN LEWISTON, M.D.:* The patient is a Mexican-American boy three and three-quarters years old who lives near Merced. He was considered well until six months before admission when his parents noted fatigue and loss of appetite. This was slowly progressive until ten weeks before admission when the patient began to have a wobbly gait, temporal headaches, and a dry non-productive cough. By two weeks before he was admitted to Stanford his fatigue and lethargy had become pronounced and he was admitted to the Merced General Hospital. There was no history of direct exposure to agricultural toxins although the area is occasionally sprayed and the patient plays in an irrigation canal. Pub-

*Pediatric Resident.

lic health records verified that he had received a full course of tetanus and poliomyelitis immunizations. An extensive laboratory work-up for metabolic or infectious processes was negative. In the hospital, he was noted to have periods of well-being alternating with somnolence and episodes of extremely shallow respirations. His parents signed him out of the hospital against advice but brought him back three days later following a spell of cyanosis, rigidity, and loss of consciousness. A repeat work-up for infection, including histoplasmin, coccidioidin, and tuberculin skin tests and titers and dark-field examinations for *Leptospira*, was negative.

The intermittent periods of somnolence persisted and he was transferred to Stanford. He had been given oxygen by mask during the trip and arrived here unresponsive with slow, shallow respirations. Blood gas studies showed pH of 7.12, PO_2 of 60, and PCO_2 of 160. A nasotracheal tube was placed and artificial ventilation begun. Considerable effort was needed to produce adequate chest-wall excursion. A pressure-limited respirator could not deliver an adequate tidal volume. A volume-limited respirator developed delivery pressures of up to 50 cm of water to produce the tidal volume required.

The patient was somnolent and unresponsive to stimulation but there were no localizing signs. There was board-like rigidity of the muscles of the abdomen and longitudinal spinal group. The rectus abdominus muscles were so knotted as to appear as subcutaneous tumors. A careful search of the entire skin surface showed no evidence of tick or arachnoid bite. The physical examination was otherwise negative.

After two hours of artificial ventilation, the patient sat up, pulled out his nasotracheal tube, and asked for his parents. He appeared to be neurologically intact except for persistence of the muscular "spasm." Repeat blood gas determinations showed pH of 7.35, PO_2 of 52 mm, and PCO_2 of 80 mm. Oxygen was given by mask. Two hours later he was again somnolent and the PCO_2 had risen to 140 mm. Positive pressure ventilation was resumed. Within 24 hours after continuous ventilation was begun and maintained, the child was fully alert and responsive. He appears to be neurologically and intellectually intact.

Laboratory work was as follows: The cell count and urinalysis were normal. A spinal tap

was bloody but was sterile to culture. Sodium and potassium were normal but the bicarbonate was 42 mEq per liter and the chloride was 88 mEq per liter. Blood urea nitrogen (BUN), glucose, calcium, alkaline phosphatase, serum glutamic oxalic transaminase (SGOT), creatine phosphokinase, (CPK), serum proteins and blood ammonia were all normal. The serum phosphorus was low (1.5 mg per 100 ml) and the lactic dehydrogenase (LDH) was high (425 units per ml). Cultures of urine and blood were sterile. Toxic screening of urine and blood were negative for organic solvents, barbiturates, amphetamines, hypnotics, fluoride and heavy metals. Serum from the patient was injected intraperitoneally into suckling mice without untoward effect. An electrocardiogram was normal. An electroencephalogram during a somnolent period showed generalized slow waves suggestive of a toxic or anesthetic state.

Continuous spasm of the muscles of the chest-wall and trunk persisted. An electromyogram of these muscles showed electrical silence, a state of contracture without contraction. Electrical stimulation of these muscles did not generate potentials. Noninvolved muscles of the neck and leg showed normal action potentials. Attempts were made to relax the contracted muscles with curare, quinidine, calcium, and diazepam (Valium®). None of these agents produced significant relaxation.

Treatment has been supportive. Human tetanus antitoxin and a tetanus toxoid booster were given. A tracheostomy was performed. Constant positive pressure ventilation has been maintained in our intensive care unit. Delivery pressures of 50 cm of water are still required to produce the necessary tidal volume.

JAMES THEODORE, M.D.:* I wonder about that PCO_2 of 160 and PO_2 of 60. Can't we ascribe those values to technical error?

DR. ROBIN: Yes, unless he were receiving supplemental oxygen, a PCO_2 of 160 mm of mercury would result in a PO_2 of about a minus 20 mm. It would be physically impossible to have true values of this range in patients breathing room air.

JEFFREY BALFUS, M.D.:** He was receiving oxygen by face mask when the blood was drawn for this sample.

*Assistant Professor of Medicine.

**Pediatric Intern.

DR. ROBIN: Would it be fair to say, as an approximation, that there was a direct correlation between the PCO_2 and his mental status? It seems to me that this was an important point in the initial evaluation when it appeared that the differential diagnosis would include some central nervous system diseases. I think it was the conclusion of those who took care of the patient that his abnormal cerebral status was largely a function of abnormal blood gases.

DR. THEODORE: What was the rationale for a trial of quinidine?

MR. MARK YZUEL:[†] Quinidine is known to slow depolarization. It has been used to produce relaxation in certain disorders such as 2, 4 - D intoxication.

DR. ROBIN: And also Thomsen's disease (myotonia congenita), although quinine is thought to be more effective.

DR. LEWISTON: I might add that methocarbamol was also used in therapeutic doses for about two days without any notable effect. This drug is a relative of mephenesin and is a muscle relaxant that has been useful in the treatment of tetanus.

DR. THEODORE: In your toxic screen there was one that was missed. You might have looked for para-nitro phenol. The patient is a migrant worker's son and may have contact with some agricultural organophosphate.

A PHYSICIAN: This doesn't appear to be an anticholinesterase type of toxicity to me. Wouldn't you expect more of a cholinergic crisis?

DR. ROBIN: There have been reports of the association of organic phosphates and muscle disease, but not of this variety. The muscle disease in organic phosphate intoxication is usually inflammatory muscle disease and seems to be associated with flaccidity rather than rigidity.

LARRY SIMON, M.D.:^{*} Have the neurology consultants been able to come up with a logical neurological lesion that would explain the picture of regionalized muscular spasm?

SEVERAL VOICES: No.

DR. ROBIN: A large number of consultants have seen this patient and each one seems to have made no less than three suggestions. I think we might focus on the established factors so that this discussion may be somewhat more cohesive. Three important features of his disease are (1) rigid muscles, (2) alveolar hypoventilation, and

(3) the requirement of high respirator pressures to produce adequate ventilation. Can we use these features to explain the respiratory failure? DR. SIMON: All three of these seem to go together in that there seems to be contracture of the respiratory muscles, producing a very low chest wall compliance.

DR. ROBIN: One of the very interesting questions in that respect is whether the patient's diaphragm is directly or indirectly involved by the primary disease. If he has an intact diaphragm, he should be able to mobilize fair respiratory volumes without too high a work cost in spite of the intercostal contraction. If you try to contract your own rectus abdominus muscles and then breathe with your diaphragm, you will encounter a great deal of difficulty in producing adequate diaphragmatic excursion. It is entirely possible, then, that his diaphragm may be normal and that the abdominal muscle spasm is restricting ventilation.

FRED ELDRIDGE, M.D.:^{*} Yes, it is important to have a relaxed abdomen to achieve adequate diaphragmatic movement. Diaphragmatic movement is a function of a pressure differential between the chest and abdomen. One interesting question would be whether his diaphragm is activated. An electromyogram of the diaphragm might be worth obtaining. This can be done in a rough way by putting an electrode down the esophagus and recording the electrical activity at the lower esophagus with a bi-polar lead. Whether or not his diaphragm is effective, we can assume that a rigid abdomen would limit its usefulness in either case. We know that in the absence of diaphragmatic activity the external intercostal muscles can support respiration. In the absence of this external intercostal activity, diaphragmatic activity would be very important.

DR. ROBIN: I take it, then, that everyone will agree that what we have here is a patient who is enclosed in a functionally tight "plaster cast" of contracted or contractured muscles that permits little movement of chest or belly. Because of this he has to exert very high inspiratory pressures which he cannot maintain over a period of time. Therefore he becomes "satisfied" with a sharp decrease in alveolar ventilation. As a result of alveolar hypoventilation, he develops severe hypoxemia, hypercapnea and acidosis.

^{*}Fellow in Respiratory Medicine.

[†]Clinical Clerk (Fifth Year Medical Student).

^{*}Associate Professor of Medicine.

These in turn produce somnolence, coma and other central nervous system abnormalities. When the energy required to overcome the restriction produced by the tight muscles is furnished by a ventilator, gas exchange becomes normal, alveolar hypoventilation no longer exists and the patients' cerebral status also becomes normal.

DR. ELDRIDGE: It is apparently very easy to fatigue the diaphragm in the face of a high work load. I wonder if that could be what's happening here. Perhaps the diaphragm can function for a while but then fatigue and hypoventilation ensues. The diaphragm is like the heart muscle in a way. It extracts a tremendous amount of oxygen and might be faced with inadequate oxygen supply if faced with too much work.

DR. BALFUS: I have a question about respiratory care in this case. I wonder if positive pressure is the best way to ventilate the patient. It appears from his chest film that he may be getting emphysematous changes. Wouldn't an "iron lung" be a better means of ventilating him?

DR. ELDRIDGE: Let me make a physiologic point. It doesn't really make any difference whether the intra-alveolar pressure is 760 mm of mercury and the intra-pleural pressure is 750 mm (in other words a 10 mm gradient from inside to outside the lung), or whether the pressure is 1400 mm inside and 1390 mm outside (still a 10 mm gradient). The only thing that matters to the lung is the pressure differential, not the so called positive pressure inside the lung. As long as you're not expanding his lung very much, you're not going to make it emphysematous. Obviously the high intra-thoracic pressures may have some effect on the venous return, but these will not affect the lung.

DR. ROBIN: The ability of most types of negative pressure respirators to generate much of a pressure differential is limited.

DR. ELDRIDGE: Physiologically the venous return is affected just as much with the whole body negative pressure respirator as with the positive pressure respirator, since in them the negative pressure is applied to the whole body.

GEORGE FISHER, M.D.:* If your model is correct, what this boy needs is a large ventral hernia.

DR. ELDRIDGE: I'd like to make another point about a pet peeve of mine and that is the concept of taking these patients off the respirator to see how they will do. My analogy is of a person

with a broken leg. You wouldn't take off his cast and tell him to walk 50 yards just so you could see how he does. I think that people who can't breathe need a respirator all of the time and not just 10 minutes out of an hour. It just doesn't make sense to take away a crutch for 45 or 50 minutes out of an hour just to see how bad a patient will get. Until something happens to improve these muscles, he should be on a respirator. I further think that you will know when he doesn't need the respirator, not by taking him off but by observing that less pressure is required for effective ventilation.

DR. FISHER: My comment about a ventral hernia was not entirely facetious. Isn't there a danger of developing a pneumothorax with these high pressures?

GRANT FLETCHER, M.D.:** Here we have a child with essentially normal lungs. I don't think the pressure will make much difference. The difference between this patient and, say, a child with cystic fibrosis is that in the diseased lung you will differentially inflate the alveoli that are open and can get a horribly distended lung very fast if you get too enthusiastic. The expansion of subunits in the normal lung occurs in a smooth and symmetric manner during inspiration. You can demonstrate this by putting a balloon in a bottle. You can inflate the balloon until you break the bottle but you will not burst the balloon. It is terribly important to watch these airways, to keep them clear and free from infection in every way you can. If you get an uneven lung, your problems are something else entirely.

A PHYSICIAN: It seems to me that in a patient with a permanent tracheostomy that the chances of avoiding an airway infection are very small indeed.

DR. ROBIN: That isn't necessarily true. In the days of poliomyelitis and long term respirator care, people who knew how to take care of these patients could keep them free of infection for very long periods. Much of our difficulty with the mechanical problems in this patient seems to be in the eyes of the beholders. We tend to become acutely uncomfortable when we see the pressure gauge swing around to 45 cm of water. However, much of this energy is dissipated in overcoming the restriction of tight muscles. We can assume that we started out with someone with essentially normal lungs and that our model

*Chief Medical Resident.

**Professor of Anesthesiology.

TABLE 1. — Disorders Associated with Prolonged Muscle Contraction/Contracture*

1. Toxins involving muscle contraction acting proximal to the muscle
 - A. Tetanus¹
 - B. Strychnine
 - C. Ichthyosarcotoxism²
2. Stiff-man syndrome^{3,4}
3. Abnormal ATP availability as result of altered glycolysis
 - A. Monoiodoacetate poisoning⁵
 - B. Heritable
 1. McArdle's disease—phosphorylase deficiency⁶
 2. Muscle phosphofructokinase deficiency⁷
 3. Rigor Mortis (ATP deficiency)⁸
 - C. Acquired
 1. Minamata Bay Disease (mercury poisoning)⁹
4. Myotonia paradoxa¹⁰
5. Relaxing factor deficiency^{11,12,13}
6. Alteration of physical state of muscle
 - A. Myositis ossificin
 - B. Diffuse muscular fibrosis
7. Vera's Disease

*This table was compiled with the assistance of Dr. Marsha Armstrong, Fellow, Clinical Pharmacology Division.

for respiratory care should be the chronic poliomyelitis patient rather than someone with severe chronic lung disease.

We might spend some time on the etiologic and nosologic features of this disorder. I'm going to propose that we are dealing with a new disease which does not fit any previously described disorder. I thought it might be useful to review the differential diagnosis (Table 1).

There are a number of disorders associated with spastic or with contracted muscles that can be thought of as being related to abnormalities occurring proximal to the muscle itself. If you stop the abnormal neuro-muscular transmission, the muscle then relaxes. These disorders include tetanus and strychnine poisoning. An interesting example is the neuromuscular disorder resulting from the ingestion of certain fish that are regarded by the Japanese as a delicacy. Ingestion of a toxic agent, contained in the fish may result in repetitive muscular contraction (ichthyosarcotoxism).

There is another group of disorders that are very interesting. The common denominator seems to be depletion of metabolic energy, particularly that aliquot of energy derived from anaero-

bic glycolysis. The model for this disease is moniodoacetate (MIA) poisoning, which I don't think has occurred in man unless perchance some biochemist anxious to collect insurance on his wife has used it. This disorder has been studied in isolated frog muscle. Monoiodoacetate inhibits the glycolytic pathway at the step between 3-phosphoglyceraldehyde and 1,3-diphosphoglycerate. A frog muscle exposed to MIA and then electrically stimulated goes into a state of prolonged contracture and is essentially not relaxable. There are several clinical equivalents of this. The best known of these is phosphorylase deficiency, or McArdle's disease. This is characterized by deficient muscle phosphorylase activity occurring as a heritable (autosomal recessive) or mutant disorder. All other enzymes in the chain of phosphorylation activation and inactivation are normal. As a result, muscle contraction depends entirely on the oxidation of glucose and fatty acids. During exercise this is insufficient to provide adequate adenosine triphosphate (ATP). But anaerobic glycolysis is not available to supplement ATP because of the deficient phosphorylase activity. The manifestations fit the biochemical abnormalities. During rest the patient is normal. With severe exercise there is muscular pain, stiffness and weakness.

Skeletal muscle phosphofructokinase deficiency, (not involving the red cell) has also been described and is a heritable disorder. At rest or with very moderate degrees of exercise, muscle tone is normal. When the patient exercises and has to call on glycolytic energy as an additional source, the muscles go into a state of severe contracture with much pain. I think that both of these disorders are ruled out in this patient by the fact that his muscles are permanently in a state of contracture, independent of energy dependence on the glycolytic pathway. There are some interesting aspects of aspects of rigor mortis which I facetiously propose as one of the differential diagnostic possibilities in this patient. One of the important changes in a muscle that undergoes rigor mortis is a sharp decrease in ATP concentration and, I suppose, a sharp decrease in ATP availability. I will be surprised if in the next five or ten years someone doesn't describe the living analog of rigor mortis in which the muscles are ATP-deficient and go into contracture when energy needs cannot be met.

A PHYSICIAN: Dr. Robin, isn't it the actinomyosin contraction that is the energy-requiring process?

DR. ROBIN: Yes, but relaxation also depends on ATP. In addition to heritable metabolic disorders, there are some acquired forms. The nearest equivalent as an acquired form is represented by heavy metal poisoning. A dramatic example of this was demonstrated in Japan near Minamata Bay. Large amounts of mercuric chloride were dumped in the water. Over a period of time, people eating fish and shellfish developed a disease characterized by severe maintained muscle contractions. Since heavy metals affect SH containing enzymes and since several of the glycolytic enzymes are of this type, it is conceivable that this disease is an acquired analog of the metabolically heritable disorders. This patient's disease is not of this type, since he has contracture as a permanent state and not during periods of increased requirement for metabolic energy.

Now there are at least two other interesting disorders that the patient doesn't fit well. Both of these involve difficulty in relaxation of a muscle once it contracts. One of these is myotonia paradoxa, (called paradoxa because exercise produces violent contractions of muscles) in contradistinction to myotonia congenita, or Thomsen's disease, where exercise improves relaxation of the muscle. Clearly our patient's disease has nothing to do with the state of exercise. The second disorder is extremely rare. There are only two patients which have been described with this disease. This disorder is considered to result from the absence of relaxing factor in the affected muscle. It is generally accepted that Ca^{++} plays an important role both in the contraction and relaxation of skeletal and cardiac muscle. When an action potential arises in muscle, there is a migration of calcium ion from the sarcoplasmic reticulum to the aqueous phase of the sarcoplasm. As calcium ions reach the sarcoplasm they cause contraction of the myofibrils and then, as the muscle becomes repolarized Ca^{++} migrates back into the sarcoplasmic reticulum. If Ca^{++} doesn't remigrate into the sarcoplasmic reticulum, the muscle will remain permanently contracted, or at least contracted for long periods.

It has also been postulated that there is a substance called "relaxing factor" which is impor-

tant for promoting flux of calcium from the aqueous phase of the sarcoplasm back into the sarcoplasmic reticulum. A patient has been described with prolonged muscle contractions, not necessarily muscle contracture. Isolated muscle from this patient showed a slow rate of calcium migration to the sarcoplasmic reticulum, as compared to normal muscle. It was postulated that this patient had relaxing factor deficiency. Moreover, it was shown that this patient generated very high lactate levels during exercise indicating that presumably the contraction phase in terms of energy generation was normal and that one had a defect in the relaxation phase of the muscle. The electromyogram of the patient with relaxing factor deficiency fit the postulated base of this disease well, in that the contraction produced by electrical stimulus was perfectly normal and it was the relaxation phase which was electrically silent.

It seems clear, then, that the electromyogram of our patient which shows electrical silence during all potential phases of activity does not fit the criteria for relaxing factor disease, either described or postulated.

There are at least two other theoretical possibilities, one of them more or less well described and the other mentioned in passing, in which one could have a significantly hardened muscle over a long period which would be impervious to the action of pharmacologic agents. One disorder is myositis ossificans, in which the muscles, for reasons which are not very clear, turn into bone. The second disorder is diffuse muscle fibrosis so that in spite of the fact that everything proximal to the muscle is perfectly normal, the muscles are hardened and can't contract or relax. There is no evidence that this patient has fibrotic or ossified muscles, at least judging by palpation, although I suppose for the sake of completeness he should have a muscle biopsy.

If I therefore take these possibilities and other suggested by various consultants, it seems likely that the dimensions of this patient's disease are substantially different from those of any previously described disorder. We have a patient who has had a long incubation period and a long course of disease. It has been present for at least three weeks and it may actually have been present for the several years of his life. This makes the possibility of an acutely acquired exogenous

agent, toxin, or infectious process unlikely. Secondly, the symmetry and the regional distribution of involved muscles are striking, although regional tetanus has been described. In particular the involvement of muscles of the thorax and abdomen with sparing of the head, neck and face is unusual. The muscles of the upper extremity are probably involved as well, since in the erect position our patient resembles a miniature Charles Atlas. The failure to produce muscular relaxation with massive doses of curare is likewise an important characteristic of his disorder. From the standpoint of scientific completeness, I think it would be useful to try to produce muscle relaxation with succinyl-choline as well. This agent blocks the neuro-muscular transmission by a different mechanism than does curare. I think the dangers of trying this would be essentially nil and it might be important to try to document succinyl-choline insensitivity.

DR. FLETCHER: There is a reason we haven't tried this. In the presence of muscle contractions, the multiple firing produced by succinyl-choline may produce a sharp rise in the serum potassium concentration. This is known to occur even in people with normal muscles and we were unwilling to take this added risk, at least until all the other systems were in good control. I think that the suggestion that this may be a relaxation problem is quite valid. One reason that the curare did not work is that its duration of action, an hour or two, may not have been long enough. Once these muscles are in this state, any continued firing of neurons may tend to maintain it. One way of producing a prolonged neuronal block would be to do a continuous epidural block anesthetic on this child and maintain it for, say, 24 hours. If so prolonged a block doesn't produce any relaxation, it is unlikely that succinyl-choline would have any effect. It is also known that in children with strange muscle dysfunctions, the use of succinyl-choline can precipitate a fatal hyperthermia although the reason for this is not clear.

DR. ROBIN: Hyperthermia caused by succinyl-choline occurs not only in children but in adults.

The use of a continuous epidural block would be a much safer way of producing the same effect, but my prediction is that nothing will happen and the muscles will remain unrelaxed. It seems to me that to call this a new disease is

not too outlandish a suggestion, and in the spirit of an old medical tradition I would propose naming it "Vera's disease," after the patient.

I think if we pull together the diagnostic and therapeutic suggestions which have been made here, these include:

- (1) Continued meticulous care of his respiratory tract,
- (2) Muscle biopsy,
- (3) To try to achieve prolonged neuronal blockade using some kind of technique,
- (4) If we assume that we will be faced with a disease of some months' duration, to evaluate the status of the diaphragm and,
- (5) To consider the possibility of surgical division of the rectus muscles in order to give him more freedom for diaphragmatic excursion.

DR. FLETCHER: That sounds like a good idea in theory, but with the spasm of his intercostal muscles, release of the intrathoracic pressure by creating a ventral hernia would very likely lead to contraction of his chest volume with a subsequent permanent restrictive deformity.

DR. THEODORE: Were there any episodes of hypoglycemia or glucosuria?

DR. LEWISTON: No. Why do you ask?

DR. THEODORE: Some patients who present with insecticide poisoning manifest hypoglycemia and show glucose and protein in their urine. I don't think that this is a good case for anticholinesterase poisoning but measuring blood cholinesterase or red cell acetylcholine esterase levels may be helpful. Some of these agents have direct neurotoxic effects.

MR. YZUEL: Since we are talking about rare metabolic disorders, I'd like to mention that there is a weak consanguinity in the parents. A great-grandparent of each of the parents were brother and sister.

DR. ROBIN: That is of great interest but he is one of eight children and none of the others seem affected. If one could propose a suitable biochemical marker for this disorder, we would certainly want to screen his family.

Are there any further questions? If not, thank you for coming.

Epilogue:

Continuous epidural block produced no relaxation of the contracted muscles. Fluoroscopy

showed that both diaphragms seemed to have adequate excursion. A muscle biopsy showed extensive granular degeneration in a random individual fiber pattern. No inflammation, dystrophy, or abnormal storage products were seen. The blood vessels appeared normal. The disease was interpreted as a primary myopathy of unknown type.

Positive pressure ventilation was maintained for approximately three weeks. Periods of up to two hours off the respirator were then tolerated by the patient although even minor exertion would quickly tire him. Although the muscles remained firm to palpation, a pressure of 30 cm of water seemed adequate for tidal volume and a pressure-controlled respirator could provide this. Attempts at walking brought about bulging of the muscles of the abdomen and thighs, resulting in a stiff gait and peculiar kyphotic posture. Domestic pressures necessitated transferring the patient to Merced General Hospital. After five months there, assisted ventilation is still re-

quired intermittently during the day and during sleep. The clinical status has shown no real improvement.

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THE RIGHT OPERATION FOR PATIENTS WITH PROXIMAL AND MID-RECTUM CARCINOMAS

My own feeling is that the abdominoperineal resection, the Miles operation, which implies a permanent colostomy, is an operation that should perhaps be the procedure of choice in the younger and good risk individuals with mid-rectum carcinoma in whom you want the very best chances of cure. On the other hand, any lesion that is 6 cm is usually amenable to either pull-through or to anterior resection, with or without diverting colostomy as a temporary measure. Certainly especially in the older age group, in people who are afflicted with Parkinson's disease or other conditions which make it difficult to manage a colostomy, providing a functioning anus is something that we ought to strive to do. Finally in the old age group, patients in their 80's and 90's, we have had very good luck with local treatment, especially for tumors that arise in the posterior wall of the rectum. I think that there is really a place for this. I can't accept John Madden's dictum that this is the procedure of choice. I don't think it is at all, but we have found that the vast majority of this older age group will outlive their tumor and will die of other causes before the tumor has a chance to recur or before metastases become widespread. So I think particularly in this group the local treatment is the preferred treatment.

—CHARLES B. RIPSTEIN, M.D., Brooklyn
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MEDICAL STAFF CONFERENCE

Endocrine Manifestations of Malignant Disease

These discussions are selected from the weekly staff conferences in the Department of Medicine, University of California, San Francisco. Taken from transcriptions, they are prepared by Drs. Sydney E. Salmon and Robert W. Schrier, Assistant Professors of Medicine, under the direction of Dr. Lloyd H. Smith, Jr., Professor of Medicine and Chairman of the Department of Medicine. Requests for reprints should be sent to the Department of Medicine, University of California, San Francisco, San Francisco, Ca. 94122.

DR. SMITH:* We will devote this Medical Grand Rounds to a discussion of endocrine manifestations of cancer. Dr. Gilbert Gordan will present the case and initiate the discussion.

DR. GORDAN:† The patient for discussion today is a 50-year-old diesel engineer who presented to his private physician with complaints of nocturia and diarrhea. Initial laboratory studies revealed hypercalcemia, a low normal serum phosphate level and a high alkaline phosphatase level. He was referred to the "Bone and Stone" Clinic at the University of California Medical Center, San Francisco, for evaluation of presumed hyperparathyroidism. On physical examination he appeared chronically ill with evidence of recent weight loss. He had an enlarged right supraclavicular node, a hard tender mass in the eighth left rib and dullness at the left lung base. The liver was stony hard and descended 6 cm below the right costal margin in the mid-clavicular line.

Serum calcium was 13 mg per 100 ml, but other serum electrolytes were normal. Acid phosphatase was not increased and hematocrit and serum protein concentration were normal. The serum concentration of parathyroid hormone (PTH) as measured by radioimmunoassay was found to be increased and equivalent to

that amount contained in 30 μ l of a standard parathyroid adenoma extract. The combination of hypercalcemia and an elevated PTH concentration is diagnostic of hyperparathyroidism, since hypercalcemia from other causes suppresses parathyroid secretion. The hyperparathyroidism could arise from a parathyroid adenoma, from parathyroid hyperplasia or from ectopic production. The clinical evidence and the immunological studies, which Dr. Roof will discuss later, indicated that we were dealing not with a parathyroid adenoma but with hyperparathyroidism due to ectopic secretion of PTH by a nonparathyroid carcinoma. X-ray examinations were of great importance and will be discussed by Dr. Gold.

DR. GOLD:* Less than 30 percent of persons with hyperparathyroidism have roentgenographic changes in the skeleton. One such change is subperiosteal resorption. When present along the radial margin of the middle phalanges of the hands, this sign is pathognomonic of hyperparathyroidism. However, in the present case neither the hands nor the other skeletal structures manifested subperiosteal resorption. Chest roentgenogram on October 11, 1969, demonstrated recent fractures of the second and eighth left ribs, a destructive expansile lesion of the right eleventh

*Lloyd H. Smith, Jr., M.D., Professor and Chairman, Department of Medicine.

†Gilbert S. Gordan, M.D., Ph.D., Professor of Medicine.

*Richard H. Gold, M.D., Assistant Professor of Radiology.

rib, fluid in the left pleural cavity and a superior mediastinal mass displacing the trachea to the left. The heart, pulmonary vessels and lungs were of normal appearance. Barium enema and intravenous pyelogram studies were within normal limits. An upper gastrointestinal study revealed compression of the gastric antrum by an extrinsic mass, possibly representing enlarged lymph nodes. By January 12, 1970, radiological studies revealed multiple osteolytic lesions of the entire rib cage. The rapid progression of the osseous lesions combined with absence of subperiosteal resorption favored the diagnosis of osseous metastasis or multiple myeloma and was evidence against the diagnosis of bone disease due to primary hyperparathyroidism.

DR. GORDAN: Of most importance to us was the fact that the films of the hands showed no subperiosteal resorption. Scans of the liver and lung showed multiple defects. Bone marrow revealed only slight plasmacytosis, but no myeloma or malignant cells. Sputum cytology showed no malignant cells on multiple examinations. Histological confirmation of malignant disease was obtained by lymph node biopsy which revealed an epithelioid bronchogenic carcinoma.

Treatment with prednisone resulted in very prompt relief of pain and correction of hypercalcemia. The patient also became somewhat euphoric. Five days later, however, he had an attack of nausea and vomiting, and the serum amylase rose to 2460 International units. Acute pancreatitis may have resulted from both the hypercalcemia and the glucocorticoid hormone administration. We subsequently followed the patient in our clinic. While he was being treated with prednisone, the serum calcium level remained normal and he had no bone pain until just before he died of cerebral metastasis.

To place this type of ectopic hormone secretion in some perspective I will outline the variety of endocrine abnormalities associated with malignant diseases. Table 1 is a partial list of humoral agents extracted from tumors. The list does not include some incompletely characterized lipids, proteins and genetic materials, nor the unidentified substances presumably responsible for cutaneous and neurological manifestations of tumors. We have had some difficulty finding precise terms to describe these humoral agents. The terms "ectopic" or "inappropriate" secretion imply a knowledge of what is appro-

TABLE 1.—*Pseudo-Humors from "Perverse" Tumors*

<i>Humors</i>	<i>Tumor Sites</i>
Parathyroid hormone-like	Lung, kidney, colon, parotid, cervix, ovary, lymphoma, liver
Calcitonin	Bronchial carcinoid
Anti-Vitamin D	Bone and blood vessel
ACTH and MSH-like; CRF	Lung, thymus, pancreas
Antidiuretic hormone	Lung, pancreas, prostate
Erythropoietin	Cerebellum
Insulin-like	Liver, adrenal cortex, large fibromas or sarcomas
Chorionic gonadotrophin	Liver, adrenal cortex, lung, esophagus
Growth hormone	Lung, endometrium
Placental alkaline phosphatase	Lung, breast, colon, ovary, pancreas, stomach, cervix, lymphoma
Thyrotrophin-like	Choriocarcinomas, moles, testis
Phytosteryl esters	Breast, thyroid, uterus, ovary, kidney

priate. For example, polycythemia with hypernephroma was described in 1929,¹ long before the kidney was found to produce erythropoietin normally. Webster defines "perverse" as "deviating from the norm"; and we are using that term not to be provocative or euphonious, but in the best interest of precise thought and expression.

The clinical findings associated with these perverse humoral secretions may be incomplete or entirely lacking. Adrenocorticotrophin-hormone (ACTH)-secreting tumors were first recognized in patients with lung cancers or thymomas because of the clinical manifestations of Cushing's syndrome. W. Hurst Brown,² a chemical pathologist at St. Mary's Hospital in London, actually described such a case in 1928, four years before Harvey Cushing's classic description of the syndrome. It was subsequently recognized that the syndrome associated with tumors was often clinically incomplete, manifested only by hypokalemia and diabetes mellitus.³ Still later, it was found that blood corticoid levels are often increased in patients who have bronchial carcinomas, adenomas or carcinoids and are without clinical manifestations.⁴ It is now known that ACTH and melanocyte-stimulating-hormone (MSH)-like peptides are found in the blood of many patients with tumors but with no clinical or chemical evidence of hypercorticism.⁵ Similarly,

just a quarter of a century after Albright⁶ had postulated secretion of a PTH-like substance from a kidney tumor to explain the associated hypercalcemia and hypophosphatemia, Berson and Yalow⁷ showed that many patients with lung cancer have immunological PTH-like material in their blood in the absence of hypercalcemia.

As a corollary, screening of the blood of suspected cancer patients for tumor peptides by radioimmunoassay may allow earlier detection and thus lead to better treatment of tumors. For example, cancers of the lung, pancreas, colon, and kidney are often discovered at an untreatable stage; these tumors are known to produce measurable peptides. Peptides might also signal early recurrence, such as in choriocarcinomas which are monitored by blood and urine chorionic gonadotrophin levels. Thus, monitoring of cancers may greatly improve therapy as demonstrated in the treatment of choriocarcinomas of women which are now often curable even when disseminated.⁸ Certain humors are specific for certain tumors.⁹ Some tumors, such as bronchogenic carcinoma, are very versatile and may harbor multiple, measurable peptides,¹⁰ as well as other, at present undefined, compounds. In contrast, PTH-like substances are seldom if ever made by human breast cancers; therefore, there has been no difficulty diagnosing coincidental parathyroid adenomas in patients with breast cancer.^{11,12,13}

In addition to PTH, certain tumors make other substances which affect calcium metabolism. Milhaud¹⁴ has found calcitonin by bioassay of bronchial carcinoids. Of particular interest are the half dozen cases of vitamin D-resistant osteomalacia or rickets due to an unknown substance from benign hemangiomas or bone tumors.¹⁵ After removal of the tumor, vitamin D resistance disappeared, and the bone lesions healed. Cushing's phenomena, clinical or chemical, may arise not only from ectopic elaboration of ACTH- and MSH-like peptides but also, as Upton and Amatruda¹⁶ have recently shown, from corticotrophin-releasing factor.

The syndrome of inappropriate secretion of antidiuretic hormone has been associated with many tumors, notably those of the bronchus, pancreas and prostate. In some cases vasopressin-like material has been extracted from the serum, tumor and metastatic lesions.¹⁷ Polycythemia occurs "appropriately" with certain kid-

ney tumors and even cysts. A tumor-elaborated erythropoietic substance producing polycythemia in patients with cerebellar hemangioblastomas seems, in our present state of ignorance, "inappropriate," "ectopic," or "perverse." There is another form of polycythemia, however, seen with uterine fibroids and sarcomas where erythropoietic activity has not yet been demonstrable.

Hypoglycemia occurs most commonly with very large retroperitoneal fibromas or sarcomas, hepatomas, or cancers of the adrenal cortex. In almost all of these tumors insulin is not to be found, but in many the rat epididymal fat pad assay recognizes an insulin-like material. Chorionic gonadotrophin from tumors of the adrenal cortex or liver produces precocious puberty in boys or gynecomastia in adult males. Rosen¹⁸ also demonstrated chorionic gonadotrophin in bronchogenic carcinoma with gynecomastia. Although growth hormone has been found in bronchogenic carcinoma, it is not clear whether it produces any clinical manifestations. The suggestion that it might be responsible for clubbing has not been substantiated.¹⁹ Similarly, the placental alkaline phosphatase, or Regan isoenzyme, which Fishman et al^{20,21} have so carefully studied in many human cancers and in HeLa cells does not at present appear to produce any clinical manifestations. Thyrotrophic activity in hydatidiform moles and choriocarcinomas was first described by Tisné²² in 1955. It is usually associated with an increase in protein-bound iodine and thyroxine levels and radioiodine uptake without clinical hyperthyroidism. Rarely, the complete clinical syndrome of hyperthyroidism has been reported with these tumors or with embryonal carcinoma of the testis.²³

Finally, nonpeptide compounds have also been found. We first extracted phytosterols and phytosteryl esters from breast cancers.²⁴ These compounds, particularly the short-chain esters, have potent calcium-mobilizing activity (some more powerful than vitamin D or even 25-hydroxycholecalciferol). Robert Brown et al²⁵ and others have confirmed the presence of these sterols in breast cancers, and Day et al²⁶ have extended the finding to other tumors. The possibility of these agents contributing to the hypercalcemia of breast cancer is under active investigation in our laboratory.

To summarize, many humoral agents have been implicated in syndromes caused by tumors,

TABLE 2.—Comparisons of Hormone-like Activities Secreted by Tumors to Normal Hormones

Hormone Activity:	TSH-like	ACTH-like	MSH-like	PTH-like
Molecular weight	Greater than pituitary TSH	Unknown. More large molecules than pituitary ACTH	Different from pituitary MSH	Similar to PTH
Bioassay activity	Positive; longer acting than pituitary TSH or LATS	Decreased in relation to immunoassay	Increased in relation to immunoassay	Not accomplished
Immunological characteristics	Differs from pituitary and placental TSH	Similar to pituitary ACTH	Similar to pituitary MSH	Differs from authentic PTH
Amino acid composition or sequence	Unknown	Different from pituitary ACTH	Unknown	Unknown

both benign and malignant. In many cases, metabolic complications result which can be of clinical importance for the patient and, in some cases, may be the first evidence of tumor. Not all tumors make all humors, a point of some diagnostic importance. It may be hoped that this phenomenon will be exploited for the early detection and better treatment of patients with cancer.

Dr. Roof will now describe recent results obtained with radioimmunoassay techniques.

DR. ROOF:* Many tumors produce hormones apparently perverse for them. Originally, development of characteristic clinical syndromes alerted the physicians to their presence. More recently, as more sophisticated and sensitive assay techniques have been perfected, a wider variety of ectopic hormones have been demonstrated in the serum, as well as in tumors of a larger number of patients. Final proof of production of the ectopic hormone by tumor has usually rested upon extraction of the tissue and demonstration that the extracted material gives the typical required effects by bioassay, chemical methods or immunoassay. Similar syndromes can arise from multiple mechanisms. For example, hypoglycemia might be produced by insulin, or by excessive consumption of sugar by large non-pancreatic tumors without immunologically identifiable insulin, or by other insulin-like substances. Stimulation of thyroid activity can be produced by thyrotrophin of pituitary origin, placental origin, or by long-acting thyroid stim-

ulators or still other thus far unidentified substances. In extracts of the tumors producing PTH-like and ACTH-like hormones the concentration of the ectopic hormone has been quantitatively minute. Quantitations of 1 to 10 μg per gram of dried tissue²⁷ (or one-thousandth to one-thirtieth of that seen in the gland which normally produces it) have been made of the concentration of the PTH-like hormone in tumors. The enormous size of the tumor compared with the normal hormone-producing tissue thus may provide amounts of ectopic hormone sufficient to produce the clinical picture. With most ectopically produced hormones, the amount of material available has so far been insufficient for determination of amino acid sequence.

Some comparisons of hormone-like activities secreted by tumors to normal hormones are shown in Table 2. At least two of the ectopic hormones, TSH-like and ACTH-like, are more effective than their normal counterparts. The TSH-like hormone found in hydatidiform moles has been shown to have a more prolonged duration of action than that of pituitary TSH, yet is not the long-acting thyroid stimulator (LATS) of Graves' disease.²⁸

Ectopically produced ACTH-like activity is frequently in great excess of normal concentrations. In such instances cortisol output by the adrenal glands may be increased threefold, and urinary 17-ketosteroids may be increased fivefold.²⁹ Nonetheless, on bioassay the activity of the ACTH-like peptide is less than would be expected from the immunoassay.³⁰ However, it is similar to pituitary ACTH chromatographically³¹ with parallel

*Betty S. Roof, M.D., Associate Research Physician and Lecturer in Medicine.

dose response curves in steroid production and ascorbic acid depletion assays, as well as having similar enzymatic and chemical inactivation.³² It also has immunological cross reactivity with normal ACTH, as demonstrated with immunofluorescence and immunoassay.³³ Recently Amatruda³⁰ reported that the amino acid content of the tumor ACTH-like peptide differs from that of pituitary ACTH. Yalow and Berson³⁴ described heterogeneity as a normal characteristic of all glandular and plasma peptides for which they have immunoassays. In the case of ACTH, two component families of molecules which differed greatly in size were demonstrated. They postulated that the larger molecule may be bound covalently to a larger peptide because the much larger molecule traversed the Sephadex column with albumin. The usual ACTH sized molecule was found in tissue extracts but not in the plasma of a patient with ectopic Cushing's syndrome due to association with thymoma.³⁴ The larger ACTH-like peptide could be demonstrated in the plasma. Thus, the apparent abnormality of the ectopic hormone might reflect a quantitative alteration in the concentrations of normal components. The greater apparent activity of these ectopic hormones may be because of lack of the normal feedback (as by dexamethasone in the case of the ACTH-like hormone³⁵) or because of loss of normal degradation, in that abnormal sequences may not be as susceptible to normal catabolic mechanisms.

MSH has been found in all tumors where ectopically produced ACTH has been found.³⁶ By radioimmunoassay, both α and β ectopic ACTH react the same as those of pituitary origin.^{37,38} In three tumors Liddle et al²⁷ found more biological MSH activity present than could be accounted for by their content of immunoreactive α or β MSH and ACTH, and it could be separated from these substances by column chromatography. Ectopically produced antidiuretic-hormone (ADH), erythropoietin and calcitonin have yet to be studied in this fashion. The amino acid content of two ectopically produced corticotrophin-releasing factors (CRF) has been determined.¹⁶ However, the amino acid content and sequence of normal CRF is not known at present.

In 1941 Fuller Albright⁶ used the term "parathyroid hormone-like substance" to explain the hypercalcemia and hypophosphatemia accompanying a carcinoma of the kidney. Collip's⁶ bio-

assay of that tumor was negative. In fact, to date no parathyroid-like material has been active by bioassay. Sherwood²⁷ noted that the concentration of the PTH-like material produced in the tumors is so small that current methods of bioassay are not sensitive enough to detect them unless extremely large amounts of tumor efficiently can be extracted and concentrated to a small volume. Since then, the laboratories of Tashjian and Munson³⁹ and Sherwood et al²⁷ have used immunological techniques to show PTH-like material in a variety of tumors originating in colon, ovary, lung and parotid gland. With the development of the radioimmunoassay for PTH, Berson and Yalow⁷ have shown elevated plasma levels of PTH in 7 of 27 normocalcemic patients with lung cancer. Sherwood et al²⁷ examined tumor extracts with their radioimmunoassay and showed the PTH-like material to be similar to normal PTH using a single antiserum.

We have examined sera from 50 patients with cancer of tissues other than the parathyroid and the breast, using a radioimmunoassay for parathyroid hormone. Of these, 25 patients had hypercalcemia and hypophosphatemia; the remainder were normocalcemic or even slightly hypocalcemic. None of the patients had uremia, a condition known to cause increased serum PTH levels. In addition, five tumors associated with hypercalcemia and hypophosphatemia were extracted and examined by radioimmunoassay. Using antiserum developed in a guinea pig to beef PTH, we found significant PTH levels in the face of hypercalcemia in 60 patients with proved parathyroid adenomas.⁴⁰ This specific assay was also used to test sera from patients with cancer (Chart 1). Values on the patient discussed today are indicated in Chart 1. Both the hypercalcemia and serum PTH levels decreased on prednisone therapy, suggesting that corticoids may have alleviated hypercalcemia by inhibiting ectopic hormone secretion. In confirmation of the results of Berson and Yalow⁷ we found that some normocalcemic patients with adenocarcinomas or oat cell carcinomas of the lung had high levels of PTH. Although other explanations are possible, the lack of hypercalcemia suggests that this ectopic PTH is biologically inactive.

We also used two antisera to bovine PTH which were developed in guinea pigs and chickens with equal sensitivity to human PTH (Chart

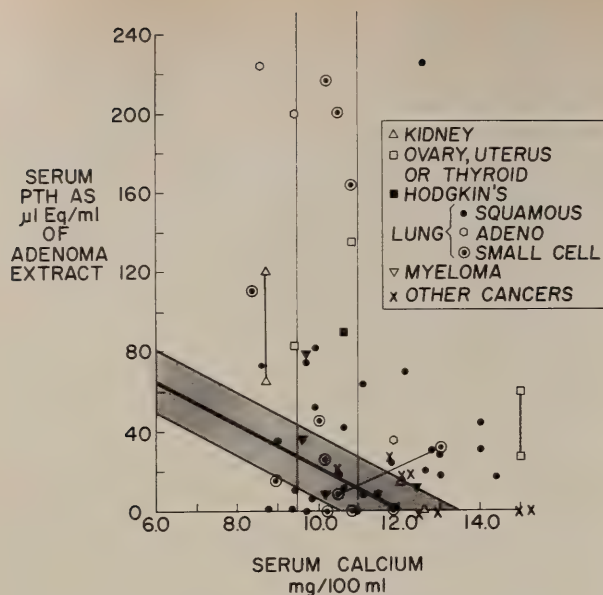


Chart 1.—Serum PTH and calcium concentrations in patients with cancer (excluding breast cancer). The patient discussed is represented by the two dots connected by a line.

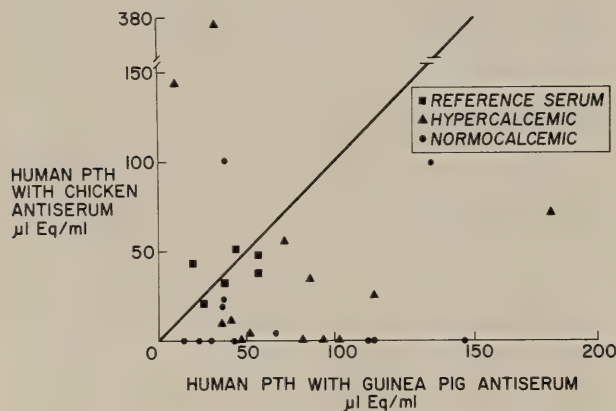


Chart 2.—Comparative measurements of serum concentrations of human PTH with two different antisera (chicken and guinea pig). Cancer patients (excluding breast cancer) had different values for serum PTH with the two antisera. (See text.)

2). With these two antisera, we have examined 26 serum specimens from patients with malignant lesions other than breast cancer. In 12 serum samples the chicken antiserum failed to recognize any immunoreactive PTH. In all but three specimens tested, the guinea pig antiserum gave higher values than did the chicken antiserum. In these three, the chicken antiserum recognized an immunoreactive PTH at three to ten times the level detected by the guinea pig antiserum. We believe that the chicken antiserum and guinea pig antiserum are reacting with different portions of the PTH-like molecule.

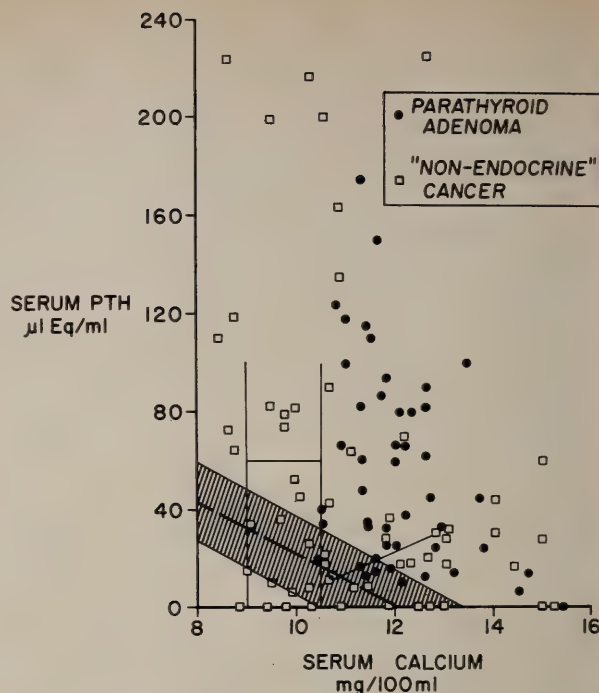


Chart 3.—Comparison of serum PTH and calcium concentrations for patients with parathyroid adenomas and patients with non-endocrine cancers. A decided overlap was observed in these two groups.

The minimal number of amino acids necessary for antigenicity is not known; however, in the case of sugars, three to five may be the minimal number.⁴¹ The fact that the two anti-sera detect different amounts of immunoreactive PTH in the sera could possibly be due to differences in amino acid sequence in the ectopic PTH and normal PTH.

Riggs and Arnaud⁴² recently confirmed and extended our claim of immunological abnormality of ectopic PTH. They also used two antisera, one developed in the guinea pig to porcine PTH and one in the chicken to porcine PTH, to evaluate 18 patients with ectopic hyperparathyroidism due to nonparathyroid cancer without apparent skeletal metastasis. Immunoreactive PTH was found to be lower in the cancer patients than in patients with adenomas of the parathyroid and similar degrees of hypercalcemia. Thus, the immunoassay could differentiate ectopic hyperparathyroidism from parathyroid adenoma as the cause of hypercalcemia in 16 of the patients. This differs from our experience which is summarized in Chart 3.

As shown in Table 3, the serum concentrations of PTH found in our patients with parathyroid adenomas and in those with overt malignant dis-

TABLE 3.—Serum Calcium Concentrations and PTH Levels Associated with Parathyroid Adenomas and Non-parathyroid Malignancies

No. of patients	Group	Serum Ca mEq/L±SE	PTH μeq/ml
60	Normal	5.0 ± .03	20 ± 2
59	Parathyroid adenomas	6.1 ± .05	57 ± 4
NON-PARATHYROID CANCERS			
26	Normocalcemic	4.8 ± .04	55 ± 7
24	Hypercalcemic, hypophosphatemic	6.3 ± .09	32 ± 5
94	Breast Cancers	4.9 ± .02	20 ± 1

ease overlapped for any level of serum calcium concentration. The mean serum calcium of cancer patients with hypercalcemia and hypophosphatemia was slightly higher than in the patients with parathyroid adenomas; however, the mean PTH level was lower than in the patients with adenomas. Interestingly, the women with metastatic breast cancer had normal calcium and PTH concentrations. This indicates that breast cancers do not make parathyroid hormone. How the PTH from cancers differs from PTH of normal, adenomatous or hyperplastic parathyroid glands is unknown. Berson and Yalow⁴³ have shown that peptides may occur in at least two families of molecules. By using two antisera, two immuno-reactive PTH's were found with different disappearance rates after parathyroidectomy. Arnaud et al⁴⁴ and Sherwood et al⁴⁵ also postulated heterogeneity for PTH in which the molecule found in the gland is larger than the secreted hormone. Thus, a variety of PTH molecules may occur normally which differ in size, and the ratio of these different sized molecules may be altered in cancers.

In extracts of five tumors associated with hypercalcemia and hypophosphatemia, we found some reactivity in the radioimmunoassay. Using these extracts thus far, we have failed to obtain curves of dilution which can be superimposed totally on those of highly purified beef PTH standard, or partially purified, human parathyroid hormone. However, estimation of PTH-like immunological activity present in our extracts agreed well with the ranges found by Sherwood et al²⁷ in the seven tumors where PTH-like activity was present. Unless it can be shown that the apparent abnormality of ectopic PTH relates to

an altered amino acid sequence, an abnormality secondary to a genetic failure or other mechanisms is not yet warranted.

In summary as numerous hormones produced ectopically have been studied by a greater variety of tests, what was thought initially to be identical with the native, or naturally produced hormone, has increasingly been shown to be non-identical. In none do we know the amino acid sequence and in only one (ectopic ACTH) is abnormal amino acid content claimed. At present more than 14 humors have been described as tumor-produced. Of these, five which have been carefully studied (PTH-like, ACTH-like, MSH-like, TSH-like and placental alkaline phosphatase from bronchogenic carcinoma) have been shown to be dissimilar to the familiar peptide. ADH and erythropoietin by existing tests have not yet been shown to be different from the normal hormone. Ectopically produced anti-vitamin D and calcitonin have not yet been studied in detail. Although the amino acid content of two ectopic CRF's has been determined, the content and sequence of normally occurring CRF at present is not known.

DR. SMITH: Dr. Gordon Tomkins will discuss possible molecular mechanisms of ectopic hormone formation.

DR. TOMKINS:* In considering this subject, decision must be made as to whether the hormonally active substances produced by certain malignant cells are normal products of those cells or represent some alteration in gene expression. Since the process of malignancy causes cells to divide in an uncontrolled way, it is capable of "amplifying" the population of any given cell on the body. Thus, if a cell which is present in small numbers in the body normally produces a hormonal substance and subsequently becomes malignant, the descendants of these cells could produce "ectopic hormones" even though the active product is perfectly normal for that particular cell.

On the other hand, it may be that cells which normally never produce hormones do so when they become malignant. Possible reasons for this aberration are legion. For instance, most cells which are not normally dividing are usually blocked in the period of cell division cycle following mitosis but previous to DNA synthesis. However, there are certain cellular products

*Gordon M. Tomkins, M.D., Ph.D., Professor of Biochemistry.

which are known to be produced only at other times in the cycle. It is conceivable, therefore, that when cells become cancerous and enter into the division cycle, parts of the genome which are normally inactive become functional as a consequence of cell division.

The basic cellular lesion which results in malignant change is not yet understood, and for the moment it is possible to entertain the idea that this aberration may somehow interfere with the normal controls over gene expression. These controls are understood, at least in microorganisms, in reasonable detail; and from our knowledge of them it is apparent that gene expression (that is, messenger ribonucleic acid (RNA) synthesis) requires that RNA polymerase attach to a particular sequence of bases in the deoxyribonucleic acid (DNA) which denote "start transcription here." In addition, the attachment of the RNA polymerase to certain genes often requires the presence of additional protein factors and small effector molecules such as cyclic adenosine monophosphate (AMP).

When the polymerase is correctly attached, transcription may not yet take place because the gene in question might be under "negative" control. That is, there may be another gene-specific protein molecule (a repressor) which blocks the action of the polymerase. If this is the case, the repressor must be detached from the DNA by interaction with a specific effector molecule called an "inducer." Once the polymerase has been allowed to begin transcribing a particular gene, regulation of this process continues since there are likewise "end transcription here" signals in the DNA as well; and these may either allow termination or be disregarded, depending on the presence or absence of additional regulatory molecules.

In mammalian cells when the initiation, elongation and termination of messenger RNA molecules has taken place, it must be further "processed" in order to become a functional template for protein synthesis. This is a complicated and largely mysterious reaction involving the removal of extraneous nucleotides and sometimes the addition of other nucleic acid elements such as polyadenylic acid. Only processed messenger appears to be transported from the nucleus to the cytoplasm where its information is translated into polypeptide sequences.

There also appears to be specific regulation as

to the initiation of the translational process. Finally, the polypeptide resulting from the translation may not be biologically active directly but must sometimes undergo "post-translational modification," a reaction in which certain amino acid residues are removed, allowing the protein to undergo changes in conformation which are required for its ultimate biological activity. In addition, many proteins are rapidly degraded intracellularly by apparently specific mechanisms. Obviously, abnormalities in any step of this complicated sequence of events could lead to anomalous gene expression—that is, to the appearance of gene products not normally manufactured by a particular cell.

Additional theoretical explanations for ectopic hormone production might be suggested on the basis of the probable viral cause of malignant disease. It might be that tumor viruses carry extraneous genetic material which is added to the normal genetic complement of the cell. In this way, although it seems rather unlikely, the expression of the exogenous genetic information could result directly in anomalous protein production.

However, it should be clear, even from this brief discussion, that before any molecular mechanism can be given serious consideration, a great deal more information must be obtained about both the ectopic hormones themselves (in particular their amino acid sequence) and the genetic regulation in human cells. Until this basic knowledge is available, speculations about the cause of anomalous protein production, although interesting, are not likely to be near the mark.

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GAMMA GLOBULIN—PROTECTION AGAINST VIRAL HEPATITIS?

Recently at the Los Angeles County General Hospital we studied a series of nurses and physicians who were accidentally stuck with needles used on patients with known viral hepatitis. In 12 such instances the patient with hepatitis was Australia antigen-positive. Five of the personnel undergoing this accidental exposure developed frank hepatitis. All 12 of the individuals having this contact received 30 ml of gamma globulin in an attempt at prophylaxis—post-exposure prophylaxis. The attack rate of 40 percent is just too high for anyone to believe that the globulin was providing any protective effect at all. In fact, one can state fairly safely that there is no evidence at all that globulin provides any protection for antigen-positive hepatitis either from person-to-person contact or parenteral forms of contact.

—ALLAN G. REDEKER, M.D., Los Angeles
Extracted from *Audio-Digest Anesthesiology*, Vol. 13, No. 7, in the Audio-Digest Foundation's subscription series of tape-recorded programs. For subscription information: 1930 Wilshire Blvd., Suite 700, Los Angeles, Ca. 90057

Important Advances in Clinical Medicine

Epitomes of Progress -- Obstetrics and Gynecology

The Scientific Board of the California Medical Association presents the following inventory of items of progress in Obstetrics and Gynecology. Each item, in the judgment of a panel of knowledgeable physicians, has recently become reasonably firmly established, both as to scientific fact and important clinical significance. The items are presented in simple epitome and an authoritative reference, both to the item itself and to the subject as a whole is generally given for those who may be unfamiliar with a particular item. The purpose is to assist the busy practitioner, student, research worker or scholar to stay abreast of these items of progress in Obstetrics and Gynecology which have recently achieved a substantial degree of authoritative acceptance, whether in his own field of special interest or another.

The items of progress listed below were selected by the Advisory Panel to the Section on Obstetrics and Gynecology of the California Medical Association and the summaries were prepared under its direction.

Reprint requests to: Division of Scientific and Educational Activities, 693 Sutter Street, San Francisco, Ca. 94102

Screening the Female Population For Gonorrhea

It is generally agreed by public health physicians and practicing physicians that there is in the United States an uncontrolled epidemic of gonorrhea of monumental dimensions. More than 100,000 cases of gonorrhea were reported in California during 1970. San Francisco has the highest rate of gonorrhea of any urban area in this country. A major problem is the existence in this state of an estimated reservoir of about 100,000 asymptomatic female carriers. For these reasons,

the CMA urges all physicians to obtain routine endocervical cultures for gonorrhea on selected populations of female patients.

The only truly reliable means for the diagnosis of asymptomatic gonorrhea in women is culture on Thayer-Martin medium or Martin-Lester Transgrow medium with carbon dioxide. Between 80 and 90 percent of gonorrheal infections in women can be diagnosed by a single culture from the endocervical canal. (Most of the remainder can be diagnosed by adding a culture obtained from the anal canal.)

It is recommended that the groups selected for routine screening should include sexually active women below age 40, especially those who are single or divorced; those who seek advice regarding contraception or sterilization; all women who appear to have cervicitis clinically; all women undergoing prenatal care, and all appli-

cants for therapeutic abortion. The yield of positive cultures will vary from 2 percent (in physicians' private offices) to 10 percent (in general clinics). The eradication of this great silent reservoir is one of the major hopes for curbing the epidemic of gonorrhea.

ERNEST W. PAGE, M.D.

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Hormonal Cytology in Office Practice

Hormonal cytology of the vagina is a reliable, inexpensive and simple semi-quantitative office procedure for evaluating normal and abnormal ovarian function. The response of the vaginal mucosa to the secretory activity of the ovary is well established. Estrogen uniquely stimulates full maturation of the stratified squamous epithelium of the vagina. The effect of progesterone is less specific but identifiable on serial vaginal smears.

The vaginal smear is best obtained from the lateral wall of the upper vagina. Smears obtained from cervical scrapings or the posterior pool of the vagina may be misleading. A routine Papanicolaou stain may be used. With a little experience, however, the physician may immediately examine the smear in his office by using one of several supravital stains (Rakoff's, Shaeffer's ink TMK 101, etc.).

Vaginal smears taken for hormonal effect must be interpreted with caution in the presence of vaginal infections, in routine Papanicolaou cervical scrapings, as a single isolated smear without knowledge of the menstrual cycle and in patients taking digitalis or steroidal hormones.

RONALD M. NELSON, M.D.

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Goldfarb AF: The cytologic diagnosis of ovulatory function. *Pacif Med Surg* 74:139-44, Mar-Jun 1966

Rubella Immunization of Adult Women: Current Status

Rubella vaccine, composed of live attenuated rubella virus, became licensed for use in the United States in June, 1969. Three vaccines are currently available for general use: Rubella Virus Vaccine, Philips Roxane Laboratories; Meruvax®, Merck Sharp & Dohme; and Cendevax®, Smith Kline & French Laboratories. Experimental trials with the vaccines, as well as clinical experience since their licensing, have indicated that there are significant differences between rubella infection, naturally acquired, and rubella immunization, vaccine-acquired. From a clinical standpoint, the important differences lie in 1) clinical manifestations, 2) communicability and 3) antibody levels and duration of immunity.

Transient joint reactions, manifested by arthritis and arthralgia, occur in 25 to 40 percent of vaccinated women, and appear to be milder with the Cendehill strain. These reactions are self-limited. Regarding communicability, most studies indicate that the vaccinated individual, although often shedding virus, is not contagious. Scott and Byrne demonstrated a lack of communicability of the vaccine virus when susceptible pregnant women were exposed. Finally, antibody levels after vaccination are significantly lower than those after natural rubella infection. Preliminary studies indicate that the persistence of antibody and duration of immunity are also less after vaccine-induced rubella than after naturally acquired (wild virus) infection.

In view of these observations, in obstetrical practice teen and adult women should be vaccinated individually: (1) blood test (HI) for rubella antibody should be obtained, particularly as part of the premarital or prenatal examination; (2) the 10 to 13 percent of patients who do not show immunity should be vaccinated, with avoidance of pregnancy for two months; (3) if the patient is pregnant, vaccination should be carried out in the immediate post-partum period (with proscription of pregnancy for two months).

Until long-range rubella immunization responses are available, it must be appreciated

that female children vaccinated early prepubertally may not necessarily be clinically immune to rubella when they reach child-bearing ages. For this reason, HI testing of teen and adult women should be performed as recommended above regardless of history of infection or immunization, while further clinical investigations are being completed.

KEITH P. RUSSELL, M.D.

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Pelvic Pneumography

Pelvic pneumography is a simple, radiographic procedure which provides an excellent image of the external contours of the uterus, the ovaries and their supporting ligaments. It is accomplished by introducing approximately 1,200 ml of nitrous oxide into the peritoneum via trans-abdominal needle puncture. With the patient in a prone inverted position on the radiographic table, the bubble rises in the pelvis to surround the reproductive organs. Appropriate films are taken. The examination is particularly useful in assessing patients who cannot be satisfactorily examined bimanually, those who have equivocal abnormalities, in differentiating uterine from ovarian lesions, and in assessing certain causes of infertility.

The primary virtues of the procedure are its simplicity and relatively low cost, coupled with a high yield of useful information. Examinations can be conducted on outpatients. No serious complications have occurred in over 2,500 examinations.

G. MELVIN STEVENS, M.D.

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Fetal Growth Retardation

Approximately one-third of low birth weight infants (less than 2500 grams) are not premature, but are term infants who are small for their gestational age (SCA). One-fifth of these infants have congenital anomalies or congenital infections. Seven percent are a result of multiple pregnancy, and 20 to 25 percent occur in mothers with cardiovascular or renal disease. In the remaining 50 percent the cause of fetal growth retardation is obscure.

During pregnancy fetal growth retardation can be suspected when the uterine fundus measured from the symphysis pubis with a tape-measure (McDonald measurement) indicates inadequate uterine growth. Antepartum death is eight times higher than normal in these patients and intrapartum death is much more likely than in normal patients. Normal 24-hour urine estriol and clear amniotic fluid (amniocentesis or amnioscopy) establish that the fetus is in no danger *in utero* for the time being.

The neonatal course may be complicated by meconium aspiration, polycythemia, hypoglycemia, hypocalcemia, pulmonary hemorrhage, or hypothermia. When a low-birth weight infant whose gestational age by examination confirms the suspicion of an SCA infant and the placenta is of normal size (450 to 500 grams) congenital defects should be suspected.

The prognosis for infants with intrauterine growth retardation, even those who do not have congenital abnormalities or intrauterine infections (rubella, cytomegalic inclusion disease, etc.), is still in question. Their weight, height, and head circumference do not reach normal levels with the first year, and long-term studies suggest that the intellectual development lags behind that of babies who have weights appropriate for their gestational age.

WATSON A. BOWES, JR., M.D.

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Minimum Evaluation of Non-Pregnant Patients with Secondary Amenorrhea Or Oligomenorrhea

Minimum evaluation of secondary amenorrhea or oligomenorrhea in non-pregnant patients should include sella turcica films, thyroid function studies, 24-hour 17-keto and hydroxysteroid urinary assays and pelvic pneumography. These examinations may not necessarily result in arriving at the specific cause of the presenting complaint but, if normal, will effectively eliminate the presence of a life- or health-threatening tumor of the pituitary, ovary or adrenal gland.

Since other causes of secondary amenorrhea or oligomenorrhea are rarely injurious to the patient, accurate diagnosis is not critical. If progressive hirsutism is present, or fertility desired, a more thorough investigation is appropriate, including therapy aimed at initiating ovulation.

If minimum evaluation is performed, the investigations, particularly sella turcica examination, should be repeated annually to diagnose the possibility of a slow-growing neoplasm.

DAVID W. KELLER, M.D.

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California Abortion Statistics for 1971

Data collected and summarized by the California State Department of Public Health show that legal abortion in California has had an explosive four years' development. The numbers performed increased each year and in 1971 exceeded 100,000 for an estimated ratio of 270 abortions for every 1,000 live births.

There are signs that legal abortions are leveling off; the rate of increase declined from its peak 3-fold increase 1968 to 1969 to a 1.6-fold increase 1970 to 1971.

Seventy percent of the patients were under age 25, and 15 percent under 17. Under age 20, 90 percent were never married, 84 percent were first pregnancies, and 40 percent used Medi-Cal. These data, along with the estimate that 60 percent of births to teen-age mothers are conceived out of wedlock, indicate that serious problems attend teen-age sexuality.

WALTER M. BALLARD, M.D., M.P.H.

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Post Oral Contraceptive Amenorrhea

In 1956 Rock, Pincus and Garcia first reported ovulation inhibition following the oral administration of synthetic estrogen and progesterone compounds. The first clinical trials followed shortly thereafter in April 1956. Prolonged amenorrhea following discontinuance of medication was not reported until 1966. The amenorrhea is secondary to anovulation produced by prolonged suppression of the pituitary-ovarian axis. All oral contraceptives have been associated with this syndrome. The incidence is, however, greater with the combination (fixed dosage) oral contraceptives.

Careful selection of patients should decrease the incidence of the syndrome. Avoidance of oral contraceptives in patients with marked menstrual irregularities and avoidance of high dosage combination oral contraceptives in patients with unproven fertility will lessen the incidence of this complication.

The practice of discontinuance of medication for one or two cycles every year or two is not of benefit. Amenorrhea has been reported following as few as three consecutive months of usage.

Unless forced by patient demands for resumption of fertility, the primary treatment is watchful waiting. It has been reported that 95 percent of patients will resume menses 12 to 18 months following discontinuance of the medication. Con-

sensus of opinion would indicate that the possibility of organic lesions, such as pituitary tumors, should be ruled out following 6 to 12 months of amenorrhea. Attempts at inducing ovulation using clomiphene or Pergonal® should be made only in patients desiring conception. These agents are not without potential complications and should be employed only after adequate studies have proven normal thyroid and adrenal function and there is some indication of normal estrogen and total pituitary gonadotropin output.

Careful selection of patients for steroid suppression of ovulation is the key to minimizing the frequency of amenorrhea following discontinuance of steroid oral contraceptives.

FREDERICK W. HANSON, M.D.

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Guidelines in Estrogen Therapy

Estrogen replacement therapy is indicated in deficiency states occurring after the menopause for relief of specific symptoms such as "hot flashes" or genital atrophy, unless there are contraindications such as breast malignancy, endometrial cancer or thromboembolic disease. Prophylactic administration of estrogens to decrease the risk of the postmenopausal occurrence of osteoporosis and coronary artery disease may be useful, but this has not been conclusively demonstrated. Balanced against any possible short or long-term benefits of estrogen are major hazards which include vaginal cancer in the female offspring of mothers receiving the hormone during pregnancy, and the increased risk of thromboembolism and myocardial infarction. Fortunately, the dose of hormone associated with complications (5 mg of conjugated estrogens, 0.1 mg of ethinyl estradiol) is generally higher than necessary. A reasonable guide is to use the lowest effective dose (0.3 to 0.625 mg conjugated

estrogens) under surveillance for any possible complications. A requirement for high dosage should be viewed with suspicion and all abnormal uterine bleeding checked by a Papanicolaou test and biopsy and by a dilation and curettage if bleeding persists after the hormone is discontinued.

KENNETH J. RYAN, M.D.

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The Case of the Vanishing Disease

To correctly treat erythroblastosis, a careful previous obstetrical history must be taken. If there were problems in the past, this will red light the possible future problems. Obtaining ABO factor, Rh, and antibody screening laboratory work is next in importance. If the patient is Rh-negative and primipara, is negative to antibody screening, and has no history of blood transfusions, a repeat antibody screen should be performed at approximately 37 weeks. If the patient has had previous obstetrical history of Rh problems or abortions, or has received blood transfusions, an antibody screen and titer should be repeated at approximately 24 weeks. If the titer has increased by a two-tube rise, then amniocentesis must be performed at that time. The optical density of the amniotic fluid is then determined and the procedure repeated every ten days to two weeks and the result recorded on a Liley grid. If the optical density level is in the non-affected range and remains there, the patient can be allowed to go to term. If on the other hand it is in the mid-zone, it must be followed carefully to determine the future course. If it does not enter the third zone until after 34 weeks but then rises to dangerous levels, delivery can be effected vaginally by induction of labor. However, if it enters the severe zone before 34 weeks' gestation, an intrauterine blood transfusion is necessary. Approximately 50 percent salvage rate has resulted from this procedure. If an Rh-

negative patient delivers an Rh-positive infant, and Coombs negative, Rho GAM® should be administered within 72 hours after delivery; doing so will completely protect the patient from Rh problems in her next delivery.

JACK R. KENNEDY, M.D.

Prophylactic Chemotherapy of Hydatidiform Mole

Molar pregnancy leads to proliferative trophoblastic sequelae in approximately 20 percent of patients; 15 percent with non-metastatic trophoblastic disease (NMTD) and 5 percent metastatic trophoblastic disease (MTD) including choriocarcinoma. The use of actinomycin D prophylactically at the time of evacuation virtually eliminates this problem.

A positive diagnosis of molar pregnancy can be made usually by the end of the 12th week of gestation on the basis of clinical signs, human chorionic gonadotrophic hormone (HCG) level, amniography and/or ultrasonography. Therapy with actinomycin D, 12 mcg per kg per day, is begun two days before evacuation (preferably by suction) and continued for two days postoperatively. Both the molar specimen and separate endometrial curettings should be sent to the pathologist for accurate assessment of malignant potential. Toxic side effects of chemotherapy are evaluated with periodic white blood cell and platelet counts even though serious toxicity is rare. Sensitive quantitative HCG tests are performed weekly until in the normal range for pituitary luteinizing hormone for three consecutive weeks. Follow-up is continued at monthly intervals for six months. Strict contraception is recommended during this time. If HCG levels plateau above normal or begin to rise, proliferative trophoblastic sequelae are likely and admission is advised.

DONALD PETER GOLDSTEIN, M.D.

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Anovulation or Oligoovulation

Treatment—Hazards and Precautions

Of the two effective agents available today, clomiphene (Clomid®) is relatively safe. The starting dose is one tablet daily for five days. If evidence of ovulation occurs, this dose can be repeated up to six cycles. If there is no evidence of an ovulatory response, the dose can be increased to two tablets daily for five days. Patients in whom there is a suspicion of polycystic ovaries should be treated even more conservatively. The first cycle should consist of one tablet daily for only three days. With this cautious program there should be little risk of ovarian enlargement and multiple pregnancy.

Treatment with human menopausal gonadotropin, on the other hand, must be highly individualized. Each patient responds differently, and patients vary from cycle to cycle. Ovarian overstimulation can be reduced by measuring total estrogen excretion daily, starting five days after initiation of therapy. The ovulatory dose of human chorionic gonadotrophin hormone (HCG) should be given when total estrogens go to 100 µg per 24 hours. It should never be given if estrogens inadvertently rise about 200 µg.

MELVIN L. TAYMOR, M.D.

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Endometrial Carcinoma and Hyperplasia

The question of the relationship between endometrial hyperplasia and carcinoma remains unsettled. Whether whatever process causes hy-

perplasia also causes cancer or results in parallel development of the two entities is unknown. There seems little risk in ordinary proliferative hyperplasia but endometrial cancer occurs more frequently associated with adenomatous hyperplasia, especially with increasing atypia, which appears to lead to carcinoma unless checked in time. Gynecologists prefer to perform early hysterectomy on these patients rather than to undertake long observation or attempt reversal, temporary at best, with prolonged continuous progesterone therapy. The frequency and importance of endometrial cancer demand that all abnormal bleeding be investigated immediately and thoroughly, for although Papanicolaou smears, endometrial washings and endometrial biopsy may be negative, dilation and curettage often reveals cancer, and high cure rates depend on early detection. One's responsibility is to prove that endometrial cancer does not exist, not that it does.

RALPH L. HOFFMAN, M.D.

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The Evaluation of Fetal Lung Maturity

The most important adjustment a newborn must make when he leaves his intrauterine environment is to adapt to airbreathing. This ability is directly dependent upon the degree of maturity of his lungs, and specifically upon alveolar stability—that is, the retention of residual air by the alveolar sacs on expiration without collapsing. When the radius of the alveolus decreases on expiration, the surface tension in the alveolus rises. Alveolar stability then depends upon a surface tension reducing complex (surfactant) lining the alveoli and lowering the otherwise increasing expiratory surface tension.

The major chemical component of surfactant is a highly specialized lecithin. Infants who develop respiratory distress syndrome (RDS) do so because of a lack of adequate synthesis of this surface active lecithin after birth. Thereby they lack the ability to retain residual air and develop the progressive atelectasis and secondary changes of anoxia resulting in the pathologic changes of RDS frequently also called hyaline membrane disease.

Since the lung is a secretory organ, it is possible to assess the degree of maturity of the lung by looking for the surface active phospholipids in amniotic fluid. The surface active fractions of lecithin and sphingomyelin (another phospholipid) are extracted, run on thin layer chromatography and measured either by densitometry or planimetry.

With gestation, all lipids, and particularly phospholipids, rise in concentration. Comparison of the concentrations of lecithin to sphingomyelin shows that until the 30th week of gestation sphingomyelin has the greater concentration and then the lecithin concentration increases above that of sphingomyelin, finally rising acutely at about 35 weeks' gestation. Sphingomyelin concentrations stay level or diminish. Ratios of lecithin/sphingomyelin (L/S) less than two by densitometric comparison predict RDS while with ratios above two the lung is mature. Furthermore, the smaller the ratio the more severe the RDS will be. For example, with a ratio less than one to one the resultant baby who will be born with severe respiratory distress with 1.5 ratio or more, the RDS will be mild to moderate. In normal uncomplicated pregnancies the gestational age and birth weight correlate with the L/S ratio. In comparing certain high-risk pregnancies with normal ones, neither gestational age nor birth weight correlate with the L/S ratio. Some diseases, for example, hypertensive renal disease in the mother, speed up the maturation of the lung so that infants as early as 29 and 30 weeks gestation have had mature lung and L/S ratios above two, yet have weighed as little as 900 grams. There appears to be some delay of maturation of lung in infants born to mothers with diabetes.

The use of the L/S ratio has become widespread as the best index for successful delivery of the baby without the dread of RDS. Further-

more, in the management of high-risk pregnancies such as chronic toxemia, one can determine lung maturation, hence the time of delivery and thereby increase the salvage of good infants.

LOUIS GLUCK, M.D.

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Stiff Muscles

MOTOR DISORDERS OF THE NERVOUS SYSTEM usually cause weakness, but lately notice has been given to a group of conditions presenting the peculiar symptom of muscular stiffness at rest. Parkinsonian rigidity and the spasticity of corticospinal tract disease have long been familiar to us, and the dreadful spasms of tetanus and strychnine poisoning have an ancient history. These last have been shown to result from the fact that the toxins interfere with normal inhibitory influences on the motor neurons of the spinal cord and brain stem. Now there are new entities appearing under such exotic titles as the stiff-man syndrome, neuromyotonia, myokymia, and contracture. Mysterious at first, they have begun to yield to analysis by clinical electrophysiological and pharmacological methods. It appears that persistent involuntary muscular contraction at rest can result from disturbances at almost any level in the motor pathways, and there seem to be characteristic clinical syndromes appropriate to the different physiological mechanisms.¹

The best-known of these conditions, called the *stiff-man syndrome*, is characterized by slowly progressive stiffness and painful spasms, affecting the axial and proximal limb muscles predominantly. As in the case of tetanus, which it somewhat resembles, the abnormal muscular activity originates in excessive discharges of the spinal motor neurons, and it can often be controlled by treatment with diazepam, a drug that blocks excitation in the spinal cord. Patients with neuromyotonia suffer progressive stiffness, without spasms, that is usually more distal in location, and their muscles are slow to relax in a way that resembles myotonia; sometimes there is a con-

tinuous, rippling fasciculation called myokymia. These symptoms originate in spontaneous discharges from the terminal portions of motor nerves, and can be alleviated by diphenylhydantoin. A rare, hereditary disorder known as the Schwartz-Jampel syndrome features myotonia as well as persistent muscular contraction at rest, dating from infancy; electromyography reveals continuous electrical activity which persists during general anesthesia but is abolished by curare.²

The Specialty Conference printed elsewhere in this issue concerns a small child in whom ventilatory failure developed because of persistent contraction of the abdominal and thoracic muscles, lasting many months. The abnormal muscular state proved to be remarkably resistant to traditional muscular relaxing agents. The reason for this failure of therapy became evident when electromyography of the contracted muscles revealed no electrical activity. Active muscle shortening without accompanying membrane action potentials is called rigor or physiological contracture. (This state is to be distinguished from the passive musculotendinous shortening, also called "contracture," which often complicates immobilization of joints.) In this kind of muscle spasm, no relief would be expected from the use of relaxant drugs that act on spinal cord synapses, neuromuscular transmission, or excitability of peripheral nerve or muscle.

Until recently, contracture was a laboratory phenomenon of mainly theoretical interest, but this mechanism has now been identified in several disease states:

1. In McArdle's disease (muscle phosphorylase deficiency), and in the similar syndrome resulting from deficiency of muscle phosphofructokinase, muscle cramps that are actually contractures result from vigorous exertion, especially under ischemic conditions. Such cramps may last up to a half-hour or so and, if severe, may be followed by signs of muscle damage such as pain, swelling, myoglobinuria, and elevated serum enzyme levels.

2. Contracture also seems to operate in the rigid form of anesthetic hyperpyrexia, provoked

by administration of succinylcholine, halothane, or other halogenated anesthetics.³ This is a heterogeneous syndrome sometimes seen as a dominant trait in families with little clinical evidence of muscle disease, but also occurring in a variety of other neuromuscular disorders as well as in Landrace pigs. Administration of the offending agent produces intense muscular rigidity, hyperpyrexia (presumably from the heat of muscular contraction), acidosis, and muscle breakdown with its consequences of hyperkalemia, myoglob-inuria, and raised serum enzymes.

3. Finally, a few patients have been found to have pronounced slowing of muscular relaxation without resting stiffness; their muscles are electrically silent during the slow relaxation, a fact that distinguishes this problem from myotonia, and there is no defect in lactic acid production. In one patient,⁴ *in vitro* assay of the ability of fragmented sarcoplasmic reticulum to accumulate calcium was considerably reduced, and the clinical disorder was attributed to this defect of the relaxing mechanism, but similar studies have not been reported in other patients with this syndrome.

None of these conditions feature prolonged muscular stiffness; the contracture is a transient event. In the case of the child with ventilatory insufficiency who is the subject of the Specialty Conference, we seem to be dealing with still another disorder. The contracture was said to be limited mainly to the abdominal and thoracic muscles and it persisted for many months, although later it appears that there was muscular "bulging" in the arms and legs with an awkward gait, so that the problem may have been more generalized. Electrical stimulation evoked no response in the shortened muscles but gave normal results elsewhere, implying a failure of the muscle action potential in the affected muscles. Without more information, it is difficult to speculate about the mechanism of muscular contracture in this patient. In the laboratory, contracture can be produced in several ways. Bathing a muscle in a caffeine solution causes contracture by inducing liberation of the calcium that is stored in the longitudinal sarcoplasmic reticulum (SR); the raised cytoplasmic concentration of ionized calcium triggers the chemical interaction of actin and myosin, and tension develops. This is similar to the normal process of contraction, but caffeine substitutes for the action

potential as the stimulus releasing calcium, and the drug prevents the SR from re-accumulating calcium as it normally does after the electrical events cease. Contracture can also be produced by chemicals such as iodoacetate and dinitro-fluorobenzene, which prevent the cellular synthesis of adenosine triphosphate (ATP); electrical stimulation of the poisoned muscle gradually causes the ATP content to fall until calcium is released from the SR, and rigor appears. A similar mechanism may operate in McArdle's disease. There is, however, no laboratory model for contracture that persists indefinitely in living muscle, and it is hard to envisage *active* shortening lasting for many months; even rigor mortis comes to an end when the contractile proteins disintegrate. A more detailed report of the clinical features of the Stanford case would be welcome, and any future physiological studies will be of great interest; so far the case is intriguing, but more puzzling than instructive. A trial of therapy with intravenous procaine might be given, since it appears to counteract contracture in malignant hyperpyrexia.

ROBERT B. LAYZER, M.D.

Department of Neurology
University of California, San Francisco

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Physicians and Decisions in Health Care

THERE ARE MANY WHO SAY that health care and medical care are much too important to be left to the doctors, and it appears that this attitude has been gaining ground. There are a number of reasons for such utterances. For one thing, medical care has become something worth having, and therefore worth more to more people.

For another, it has become much more complex and expensive, and this has progressively involved a great variety of health professionals and third parties of various kinds in many aspects of medical and health care. Physicians and the medical profession as a whole have of necessity delegated many decision-making responsibilities to other professionals and in the course of time have surrendered or abandoned many more. The result of all this is that many decisions affecting patient care and the delivery of services are now being made without physician participation, often by persons or parties seeking greater power and more decision-making responsibility.

Among those who seek or assume greater sway in the making of such decisions are many in allied health professions. The trend toward separate licensure for many of these gives rise to the likelihood that a variety of professionals with quite different levels of training and competence will soon be authorized to perform identical services. Multiple levels of quality in patient care and greater fractionation will be an inevitable result of this. In the delivery of medical services there are many more kinds of decision makers and their interests are apt to be more concerned with overcoming barriers to access or continuity of care, or providing more services at less cost, or with prevention, in the illusory hope that health care costs can be significantly improved if preventive measures are effectively used. Those with interests such as these have tended to focus their decision-making more upon the needs of the system as such than upon what individual patients need and want, and to be governed by broad social or economic considerations.

In the area of overall responsibility for health care there are many others who aspire to power and decision-making responsibility. Physicians and other providers have either abrogated their decision-making responsibilities or were pushed aside, depending upon one's view of it. Social workers, social scientists, public health professionals, those who pay the bills and even educators have all been trying their hand. So far none have succeeded. More recently, and in a kind of desperation, society and its government appear to have turned to the consumer, the user of services, hoping that his natural wisdom and closeness to the need will somehow find the so-

lutions. But while consumers have made important contributions, it is becoming evident that they too really lack the skills, knowledge, experience and expertise to solve the problems. And the politicians who have the most power of all have tried, and most would agree that their track record so far in health care has been quite unsatisfactory in that their legislation has too often created more problems than it has solved.

Out of all this there may be some lessons to be learned. Perhaps most important is that none of these groups, including the medical profession, have been able to solve the problems of health care alone, no matter how hard they have tried or how much power they have. The problems of health care are unlikely to be solved without real participation and collaboration among all these groups. This light is only just beginning to dawn. All those properly concerned must be represented in the planning, decision-making and evaluation processes in medical and health care. Only as this light grows brighter, and physicians, the medical profession, other professionals, social scientists, economists, payors, public health workers, politicians and consumers begin to recognize their various roles and responsibilities, will there be real progress. As this is done, and as those who must carry out or use or finance a plan or program participate somehow in forming, operating and evaluating it, it will become their program and they will be for it, not against it, and they will have a stake in its success. This too is a lesson to be learned.

The Sixth Progress Report of the Committee on the Role of Medicine in Society, published elsewhere in this issue, makes the point that physicians and the medical profession must become competent and prepared to participate in decision-making at all levels of health care. Seldom will they be making the decisions alone. But without participation by physicians and the medical profession, the decisions reached may often if not usually lack the realism or validity essential for success. Experience has shown this to be true. Medical care and health care may be too important to be left to the doctors, but by the same token doctors cannot safely be excluded from the decision-making processes. This is a lesson to be learned by both medicine and society.

—MSMW

A Trend To Be Reversed

THE EXCELLENT ARTICLE by Beljan, which appears elsewhere in this issue, documents the dependence of this nation and the State of California upon the foreign medical graduate. It also documents the fact that the foreign medical graduate, be he American-born or not, is on the average simply not as well-trained as those who have been graduated from American schools. The extent of the dependence, and therefore the number of foreign medical graduates who will be practicing particularly as family physicians (since they are being encouraged to enter these programs) is disquieting indeed.

Since 1910 the effort in this nation has been to raise the standards of medical education. The tools have been those of accreditation, certification and licensure. This has been remarkably successful, so successful that it eventually produced a "brain drain" from foreign countries to American medical centers. It also created an enormous demand for medical education in this country which could not be met. And now paradoxically we find ourselves eroding the very standards of quality and excellence which have placed us in the forefront, and this too is disquieting indeed.

There is little that can be done instantaneously to correct this situation. The selective "brain drain" of yesteryear has become transformed into an unseemly dependence upon importing graduates of foreign medical schools. This is an unhealthy, even dangerous trend, which must somehow be reversed.

—MSMW

UNILATERAL SWELLING IN THE NECK

What procedures would you use to investigate a unilateral swelling present for six weeks and continuing to increase in size in the neck of a 45-year-old patient?

Eighty-five percent of the time anyone over the age of 45 with a mass in the neck has some type of neoplastic metastasis from an area above the clavicles. With this in mind, the last thing you should do is biopsy it. Undoubtedly the first things to do are: the usual good external physical examination, certainly nasopharyngoscopy . . . , a pharyngoscopy, and laryngoscopy. One may well consider the upper esophagoscopy and bronchoscopy. Of course, the usual chest film should be employed.

Remembering that 15 percent of the cases might be metastasis below the clavicle, you might consider the renal pelvis which is squamous in nature. Eight percent of all gall bladder tumors metastasize to the cervical neck.

If your complete examination very carefully done is negative (I am assuming you have had sinus films and the usual otolaryngologic work-up), I would *re-do* it. . . . I think that if another examination (perhaps done by a colleague) comes out negative, you are forced to biopsy the mass. Remember that this should probably be done by the man who is going to treat the patient definitively.

—DONALD A. SHUMRICK, M.D., Cincinnati
Extracted from *Audio-Digest Otorhinolaryngology*, Vol. 4, No. 9,
in the Audio-Digest Foundation's subscription series of tape-
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LETTERS *to the Editor*

Comments on Traffic Medicine

To the Editor: In the traffic issue of CALIFORNIA MEDICINE, the articles cover familiar ground. Each author has his own pet remedy. Caution the driver. Improve his harness. Motivate the alcoholic. Admonish the young. Screen the near-sighted. Straighten the highways. Pad the dashboard. Buckle the steering column. Get more ambulances. Teach more first aid. Etc., etc.

What I want to point out is that we have been doing all these things for years—with negligible results.

Nowhere in all this wordage did I see any mention of a much more fundamental attack on the problem: gas rationing. The assumption always is that driving is a necessary component of American life, not to be tampered with under any circumstances.

To be sure, *some* driving is necessary. But a whole lot is not. Let me quote two figures you rarely see mentioned: (1) Over 60 percent of all trips are less than five miles. (2) At least 30 percent of all driving is for frivolous (that is purely recreational) purposes.

Gas rationing would be inconvenient but it would not cause the collapse of our civilization. On the contrary. As doctors, we should stress that the car is a major threat to public health, just like cancer, heart disease, and stroke.

Isn't it odd that we would rather spend millions futsing around than take the bull by the horns?

CLIFFORD L. GRAVES, M.D.
La Jolla

To the Editor: The current issue of CALIFORNIA MEDICINE (February 1972) devoted to Traffic Medicine is outstanding. In particular, I appreciate the emphasis that you have placed on the magnitude of the traffic safety problem.

Comparing it with the Vietnam war deaths puts it in a perspective that has long been neglected.

There is no longer a question that at least 50 percent of fatal auto accidents are caused by the ingestion of alcohol. In particular, fatal accidents in young adult males has even a higher correlation with alcohol ingestion (66 to 75 percent). So at least 27,000 of the 54,000 auto accident deaths are directly related to this factor.

Many of the younger generation, and even many of the more responsible sociologists and scientists studying the marijuana problem, are using a logic that "marijuana is really no worse than alcohol." But isn't 27,000 deaths a year enough?

ALBERT E. WARRENS, M.D.
Chico

To the Editor: I have greatly enjoyed your Special Issue of CALIFORNIA MEDICINE, February 1972, particularly the editorial "Traffic Medicine."

Your comparison on the cover of one year of motor vehicle, U.S. casualties with Vietnam War total casualties, 1961 to 1970, is solidly impressive.

ELMER BELT, M.D.
*Clinical Professor of Surgery/Urology
University of California, Los Angeles
School of Medicine*

To the Editor: The recent symposium on traffic safety was excellent but omitted mention of one thing which I believe is very important, viz. the importance of identifying an automobile involved in any breach of the law along with the responsible owner. This can easily be established by the license number. Easy, that is, if the license plate is observed under good illumination at a distance of less than two car lengths and if the plate is not recessed, battered or otherwise obscured. This is best accomplished by kneeling behind the car with a flashlight!

Daily press reports speak of the car which escapes from a hit and run accident, a robbery,

etc. which is described by a number of witnesses as different makes, models, colors but, for very good reasons, not by the license number. The British and most European countries have larger and more legible plates which readily afford instant identification. I can well imagine the anguish of manufacturers and state agencies if larger and more legible license plates were made obligatory but this would accomplish a great deal for driver responsibility and law enforcement and would probably be welcomed by the local police and highway patrol.

EDWARD B. SHAW, M.D.
Department of Pediatrics
University of California, San Francisco

It's Blood—Not Soup

To the Editor: "If we can impose strict liability upon a restaurant serving contaminated soup, certainly we can impose a similar standard on hospitals dispensing blood."

I am sure that Assemblyman Sieroty (D, Beverly Hills) has good intentions with his transfusion bill (AB 285). However, to equate blood with contaminated soup, or even borscht, is unreasonable. The above-quoted statement from Mr. Sieroty's news release of 2 February indicates his lack of understanding of transfusion and hepatitis problems.

Mr. Sieroty is conservative with his statement, "Hundreds of persons yearly contract hepatitis as a result of transfusion of contaminated blood." In fact, there are over 30,000 *reported* cases of transfusion hepatitis with 5 to 10 percent mortality. The principal source of this hepatitis is commercial blood obtained from Skid Row donors.

Of course there is a need for research to improve detection and elimination of hepatitis virus, and to make transfusion safer. However, it is unjust to penalize hospitals and physicians for the present inadequacy of medical science.

It is suggested that Mr. Sieroty, other politicians and MDs visit the Skid Row blood collection centers. It is urged that the news media and legislators be contacted to abolish commercial, for-profit blood banking. This will be in accord with my CMA resolution (131-72), which was ably supported by Professor J. Garrott Allen of Stanford and approved by the CMA House of Delegates at the February 1972 session.

ALBERT FIELDS, M.D.
Los Angeles

Methadone is Controversial

To the Editor: The article and the editorial on the subject of methadone maintenance for opiate addicts which appeared in the February, 1972, edition of CALIFORNIA MEDICINE, neglect some very important facts and misrepresent others.

First, the article never mentions the basic rationale for methadone maintenance. The rationale for methadone maintenance is that it is supposed to reduce the number of robberies, burglaries, and other thefts that heroin addicts commit in order to get the money with which to purchase heroin. The rationale is that if methadone is supplied to opiate addicts through legitimate channels, then the addicts will not have to steal to secure the funds to purchase heroin, all of which is supplied through an illegal market at an enormous profit to the suppliers. Hence, methadone maintenance is an attempt at a medical solution to a criminal or social problem.

Thus, it follows that the success of methadone maintenance depends not upon the number of addicts that can be kept in methadone maintenance programs, but rather it depends upon whether this new form of supplying the opiate to the addict will actually result in a decrease in the amount of property stolen by addicts.

It is no medical achievement to supply an addict with a substance to further his addiction. However, it *would be* a great feat of social engineering if one could somehow lower the crime rate, but we have yet to see any sort of research project wherein there was some kind of scientific attempt to see whether methadone maintenance did indeed cut down on the amount of thefts committed.

Not too long ago, there was some improvement noted in the crime rate in Washington, D.C., and some were quick to attribute this to the instituting of methadone maintenance. It should also be noted that simultaneously with these developments was an expansion of the local police force from around 3,000 officers to around 5,000 officers.

Although there are some pharmacological advantages to one's being addicted to methadone as opposed to one's being addicted to heroin, these are pharmacological advantages only incidental, and it is the method of supplying the opiate which is the significant issue.

This whole issue becomes a *medical* problem only insofar as physicians are required by law to

prescribe such drugs as opiates. By substituting legally prescribed methadone for illegally obtained heroin, we are not "solving" any sort of "medical problem." We are only making legitimate an addiction to opiates.

Those who voice such great enthusiasm for methadone maintenance should periodically remind themselves that they are not "treating" addiction. They are merely regulating the source, supply, and content of the addicting substance.

Moreover, they might well ask themselves what effect the prospect of eventually getting on methadone maintenance (that is, the eventual prospect of a reliable, dependable, and legal supply of an opiate) has on that large, but unknown, number of young men who are experimenting with heroin and who may go either way; become addicts or abandon the use of heroin as risky and self-destructive. We already know that with these people, the more readily is it that heroin is available, the more likely is it that they will become addicted to it, rather than abandon the use of heroin. Would not the prospect of dependably available methadone have that same effect?

That is to say, is not the prospect of eventually getting methadone maintenance serving to encourage individuals to experiment with heroin rather than to discourage them from doing so?

YEHUDA SHERMAN, M.D.
Oakland

Rising Cost of PG Study

To the Editor: Postgraduate medical education, always desired, has now become mandatory. Some states already will cancel a physician's license if he fails to put in a certain number of hours of postgraduate study.

By sheer coincidence (or is it really?), the cost of postgraduate courses is shooting up. Not long ago most postgraduate course fees were between \$10 and \$20 per day. Now it is rare to find a course that costs less than \$30 a day and \$40 a day courses are not rare. A few even run up as high as \$50 a day, or \$250 a week. When you add to this the cost of travel, hotel bills, meals and possible loss of income, the cost of postgraduate education is indeed high.

I am aware that many postgraduate education activities are free, but also there is no denying that many of the most desirable courses are

given by the medical schools, and they are showing an almost exponential rise in fees.

Doesn't it sound just a little bit like exploitation of a captive customer, the practicing physician?

C. A. DOMZ, M.D.
Santa Barbara

An Ethical Issue

To the Editor: I had the pleasure recently of reading the CMA NEWS and learning that by edict of the CMA Council I am, in a 24 hour period, converted from ethical to unethical. This, if I don't tell patients that I own an interest in a hospital and because of this they may go elsewhere.

No one has bothered to ask why many physicians have elected to invest in hospitals. There are matters of the convenience of having all of your patients in one location—a time saver; the ability to exert your influence to insure efficiency in both cost and wasted time. For profit, hospitals must excel here to remain in business. The knowledge that if we are forced into a hospital dominated type of practice, as contemplated by Ameriplan and the insurance companies, then those of us practicing in a hospital environment with our "peers" in control may rest easier at night. In the past some of our colleagues have occupied the position of the chosen few in so far as the availability of hospital beds and this has led to ownership self preservation insuring beds for our patients. Surveys have shown that hospitals ranging in size from 99 to 150 beds are more economical, and many of us feel they offer more personalized service to our patients.

I do tell my patients that I go to specific hospitals for my convenience. I could site specific instances of problems that have arisen in the past causing me to take this action. I do not believe such would be in the best interest of either the hospital or the medical profession. As long as the hospital I send my patients to offers services as good as or better than other hospitals in the community in the field I practice in, I shall not specifically post a sign asking for prolonged discussion stating that I invested my hard earned money in the hospital I patronize so I can deliver better health care to my patients.

R. G. REAVES, M.D.
Santa Ana

Special Article

Preventive Psychiatry in Public Health

NORMAN Q. BRILL, M.D., *Los Angeles*

FOR MANY YEARS IN TREATMENT of patients with psychiatric disorders a great deal of emphasis was placed on defining the elements of an individual's personality that contributed to his own maladjustment. The genetic basis for the unique emotional reaction pattern was subjected to intensive study and great efforts were directed to determining the early life experiences that played crucial roles in the patient's later adjustment and behavior.

Along with the wave of increased expectations that characterize society today in the United States there was a turning away from investigation of intrapsychic factors in emotional illness to the more obvious current societal stresses that had been ignored for so long.

The Social Engineering Approach

There developed an increasing preoccupation with the role of prejudice, poverty, and other stresses and deprivations in causing mental illness. Community studies that seemed to indicate a higher incidence of mental illness in lower social classes stimulated the hope that by eliminating the lower social classes (or at least the lower standard of living that characterized them) mental illness could be substantially prevented. The borders between sociology and psychiatry became blurred and the role of psychiatrist became somewhat confused.

While I am wholly in agreement with the urgent need for greater emphasis on developing

preventive programs in psychiatry, the present trend to concentrate on social stresses has two potential complications: (1) individual treatment of patients will deteriorate, and (2) expectations that mental and emotional illnesses will be eliminated, will not be fulfilled. With regard to the first point—deterioration in individual treatment: the development of community psychiatry programs has been associated with a decreasing interest on the part of psychiatrists in the elements of an individual's personality and life pattern that contribute to his maladjustment or difficulties. Intensive individual treatment is belittled as old fashioned, wasteful, ineffective and impractical; while crisis treatment, short cuts, brief therapy, and all sorts of innovations are being offered as panaceas.

In addition the increasing preoccupation with the role of social inequities has prompted an increasing number of psychiatrists to devote their efforts to the elimination of these social stresses rather than to the treatment of the large number of patients who are in need of help. In fact, as the role that certain ecological and socio-economic factors play in illness is increasingly recognized there is more and more insistence by some that the physician has a responsibility to *lead* the campaign to eliminate them.

There are others who are not as convinced that this is the proper role for psychiatrists. As human beings and citizens they should certainly be concerned about the evils and deficiencies of society but they do not see themselves playing such primary roles in eliminating them. They tend *not* to believe that the alleviation of such

Dr. Brill is Professor of Psychiatry, School of Medicine, Center for the Health Sciences, University of California, Los Angeles.

Reprint requests to: N. Q. Brill, M.D., Department of Psychiatry, School of Medicine, University of California, Los Angeles, 760 Westwood Plaza, Los Angeles, Ca. 90024.

external societal stresses will affect the predisposition that is so crucial a factor in the breakdown of most patients. Those who have worked intensively with psychiatric patients have had opportunity to see how much interpersonal friction, unhappiness and conflict exists within families that are not underprivileged, and the divorces, alcoholism, drug abuse, depressions, psychosomatic disorders, neuroses and psychoses that result.

There are still vast differences of opinion among sociologists concerning the role that low socioeconomic status or other concomitant variables of poverty play in the development of mental disorders. While ecological studies have clearly shown that incidence rates for mental disorders in the United States are highest in areas populated by groups of low socioeconomic status, it has not yet been clearly established whether this is the result of excessive stress (direct or intrafamilial) of the poverty condition or of downward drifting of mentally disturbed persons. It is interesting to note in reviewing the dynamic formulations of patients' illnesses that are contained in the hospital chart summaries, that poverty was rarely, if ever, mentioned as a cause.¹

Rogler and Hollingshead² in a study in depth of a sample of extremely poor families in Puerto Rico were unable to distinguish any economic, familial or environmental factors that contributed to the development of schizophrenia in some patients as compared with others who were not schizophrenic. The schizophrenics had not been exposed to greater hardships or more economic deprivation from birth until their marriages than non-schizophrenics. In a study of a state hospital population, social class was found to have little effect on the degree to which patients felt their poverty and material deprivations (food, clothing, and housing) had contributed to their illness. There was a suggestion that downward social mobility in adulthood involved more mental suffering than the experience of poverty just in childhood. Furthermore, for some persons poverty does not always have a negative effect; it is a stimulous to greater effort.¹

While there is no question that poverty is often associated with excessive intrafamilial stress, undernourishment, poor physical health, and negative attitudes toward life, it is quite clear that poverty is neither necessary nor sufficient

to produce mental illness; nor is racial prejudice. Obviously all the poor and all those who are victims of racial (or religious) prejudice do not end up with disabling emotional disorders.

I would be interested in learning if psychiatrists in very poor countries see poverty as an etiologic factor in mental illness as often as do those in more affluent countries? Is it the existence of poverty in close proximity to affluence, or is it the rising expectations of poor people who can see prospects of improving their condition that creates the crucial stress?

Dr. L. B. Gold³ pointed out, "It is as unscientific to say that poverty breeds mental illness as it is to say that wealth prevents it."

Those who assume that the elimination of these stresses is the answer are to be praised for their humanitarian concerns, but in the light of the inability of people to get along with each other, the international suspicions and hatreds that are fostered by governments, human greed, envy, power-seeking, prestige-seeking and competitiveness along with the increasing demand for immediate gratification, and the decreasing tolerance for compromise, postponement of satisfaction and self denial, it is only reasonable to question the reliance on such idealistic goals as the main thrust of a preventive psychiatry program.

To achieve the solution of the many distressing problems of society, self concern will have to be replaced by continuing consideration for others. Will those who truly have had the same opportunities others have had, and not taken advantage of them, be content when they end up having less, or will they rationalize their failures and blame others? Will it be possible to provide both individual freedom to pursue instant gratification and the cooperation with, and consideration for others? Will there be acceptance of the lower standard of living that will result from the elimination of personal gain from those who are willing to work more?

Gorman and Ziferstein found that prevention of mental illness was of major importance in the Soviet Union. They said that measures taken to eliminate or reduce anxiety among people include full employment, material security in case of illness or old age, free medical care for all and free higher education.⁴ What was not said was that individual needs are subordinated to the country's needs, that individuals are ex-

pected to contribute to the common good and that the major goal of treatment is to maximize individual effectiveness. Parents have responsibilities to rear their children in a manner that will insure their conforming to their society.

If satisfactory adjustment to society without mental disorder is the goal, perhaps we need to face the fact that there are many parents (one or two as the case may be) who are not capable of rearing children to achieve this goal and that there is need to provide massive governmental programs of rearing future citizens by professionals (unacceptable as the idea may be).

Going to the other extreme, Dr. Albert S. Norris, professor of psychiatry at the University of Iowa, maintains that the predilection of psychiatrists today to seek social solutions for the problems of the mentally ill is a monumental mistake for which future generations will pay.⁵ He points out that if an exclusive social model of mental illness had been adopted 20 years ago and all effort directed toward the elimination of environmental stress, research that made modern drug treatment possible would never have been done and state hospitals would be twice as large as they are now.

It appears, then, that neither the elimination of social stresses nor concentrating on better methods of treatment of the mentally ill is going to solve the problem.

What is needed is a combination of preventive psychiatry and clinical psychiatry. A preventive program that is designed to eliminate social stress will require, in addition to psychiatrists, many non-medical specialists who are intimately involved in fields related to the prevention of illness and maintenance of a community's health. They include economists, sociologists, statisticians, lawyers, political scientists, psychologists and others.

Current social stress is not confined to racial prejudice and poverty. Unemployment, inadequate housing, malnutrition, lack of transportation, and recreational facilities, legal assistance, clothing, and even clean air and water are stresses that take their toll. Add to that list uncontrolled crime and violence, national and international tensions and hatreds, and it becomes obvious that psychiatrists alone cannot solve these problems.

The dramatic increase in the number of psy-

chiatrists and emphasis on mental health these past 25 years has not been accompanied by any visible decrease in mental illness, crime, human unhappiness or world tension.

Psychiatrists who are interested in public mental health (rather than in treating patients) will require an education that entails much more than is included in most so-called community psychiatry programs. To avoid the temptation of oversimplistic solutions and undesirable and uneconomical differences of effort a psychiatrist must acquire broader knowledge than he now has and become part of a team that provides the breadth of competence that is essential for finding solutions.

Health Care vs. Medical Care

When it was recognized that typhoid fever was caused by an infection by the typhoid bacillus and when sources of infection were identified, it was not the physician's role to do the work of the sanitary engineer or public health officer. Public health involves a great deal more than treating patients. It is involved in prevention and as such involves activities that vary from testing milk and inspecting restaurants to administration of vaccines.

Likewise it is not the psychiatrist's job to plan the country's economics. It is not his job to be the welfare worker and to determine the amount of financial or other non-medical help that a family needs. There are others who are more knowledgeable and competent to do this.

It is not primarily the physician's responsibility to see to it that landlords provide adequate heat to apartments, or that toxic paints are not used on toys, or that the migrant farm worker is paid an adequate salary.

The Implications for Education

As was pointed out by the Study Committee of the University of California's 26th Faculty Conference held at the University of California Irvine Campus on March 23, 1971 (which was concerned with professional education) few of the great issues of our time—poverty, pollution, health care delivery and others—fall neatly within the boundaries of a single discipline. Methods must be found to permit a multi-disciplinary approach to social problems. For example, the attack on the problem of pollution at UCLA has

been shaped by members of the Departments of Biology, Chemistry, Earth Sciences, Engineering, Law and Economics.

In the environmental science program each student is required to spend a year of training in solving environmental problems as a member of a team made up of persons from different disciplines. The team meets regularly with five or six faculty members from participating departments who provide guidance from their particular discipline.

A similar approach should be made to some of the pressing socio-medical or mental health problems that are attracting so much attention. Interdisciplinary programs involving economists, sociologists, political scientists and others need to be developed. Psychiatrists can contribute their expertise while recognizing that others are needed to define and to solve the complexities.

Such programs will open new career opportunities for psychiatrists as part of a public health team and eliminate the temptation to presume that they know enough and are capable enough to have the solutions to the world's problems.

Only through interdisciplinary research will the documentation be obtained that hopefully will lead to the socio-political action that will be necessary to develop a true preventive psychiatry program.

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AUDIO-DIGEST ANNOUNCES NEW SERIES FOR PSYCHIATRISTS

Commencing in the late summer of 1972, America's more than 20,000 psychiatrists will have a new and unique continuing education medium available for home, auto and leisure study.

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"The great advantage of this service," Editor-in-Chief Thomas H. Brem, M.D., said, "is that our editorial staff does extensive scanning of 600 medical journals and attends and records more than 200 national meetings throughout the year. Then, in an hour of easy, informative, practice-useful listening, they pass on to the subscriber all that is new and important in his ever-changing clinical practice picture."

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Medicine in Society

The Physician and His Practice 1980 to 2000

Sixth Progress Report of the Committee on the Role of Medicine in
Society, California Medical Association

Members of the Committee on the Role of Medicine in Society, together with medical student representatives of the medical schools in California worked for a period of close to two years preparing this Sixth Progress Report. Names of the committee members, ex-officio members, consultants and medical student members who served during the discussions and the drafting of the report are listed on the final page.

I. Introduction

UNTIL QUITE RECENTLY, THE PRINCIPAL interface between medicine and society occurred between the individual physician and his patient. A good doctor-patient relationship gave satisfaction to both. The physician was supposed to "do his best" and the patient was supposed to "cooperate" and this was all that was required of either. But now there are new dimensions to this interface. There is a widespread belief that much crisis care could be avoided if measures of prevention and health maintenance were adequately used by the medical profession. There is a general expectation that the results of modern medical care should be good, and if not, then someone must be at fault. There are public pressures

for physicians to prove that they are keeping up with scientific progress. And physicians are being asked what they are doing to bring the technical advances of modern medicine to a larger portion of the population and what they are doing to improve the health of society as a whole and why it is all costing so much with so little apparent in the way of results to much of the public. While many physicians believe that many of the expectations and demands of the public are unreasonable and at present unattainable, much of the public believes that if physicians and the health care system are pressured enough they can and will deliver care to meet the public expectations.

It is against this background that the Committee on the Role of Medicine in Society has addressed itself to "The Physician and His Practice—1980-2000." Since the committee is composed of eight medical student leaders, chosen by their peers in the eight medical schools in

Transmitted by the Council to the House of Delegates of the California Medical Association, which urged early publication of the report in *California Medicine* and directed that it be referred to appropriate CMA Commissions and Committees for recommendations on implementation.

Reprint requests to: Committee on Role of Medicine in Society, California Medical Association, 693 Sutter Street, San Francisco, Ca. 94102.

California, and an approximately equal number of experienced leaders in medical practice chosen by the Council of the California Medical Association, it seems uniquely adapted to approach this subject. The students of today will be in active practice in the years 1980-2000 and the professional leadership of today will be making decisions now which will affect their practices in 1980-2000.

II. Some Powerful Determinants for 1980-2000

The committee first identified a number of forces which it believes are certain to cause important changes in health care and thus inevitably influence the physician and his practice in the years ahead. If these are projected to 1980-2000 they may serve to give some clue to what may be anticipated in health care and for practicing physicians. The forces which seem to be the most important to the committee may be classified as conceptual, logistical, ethical and regulatory.

A. Conceptual Forces

(1) *The right to health care*

Society through its government has decided that health care shall be the right of everyone and it now appears to be determined to move toward the goal of making a high standard of health care available to all without significant barriers, although it has yet fully to recognize and admit the cost which will be involved. The obstacles are formidable and physicians and society as a whole are groping for solutions. There is certain to be confusion at least until it can be determined what the ingredients of the health care are to which everyone has a right, and where the obligations and responsibility lie in the exercise of this right. To what extent is the person or is society responsible that an individual seek access to health care? To whom is the physician responsible—to the patient, the payer, the government or society as a whole? Since society appears to have accepted the principle that health care is a right, it must soon accept and assign the responsibility for seeing to it that the principle is applied and finally give whoever is responsible the authority necessary to fulfill the assigned responsibility. There will be important decisions in the years immediately

ahead. The concept of the right to health care will be a powerful determining force and a dominating influence on health care in 1980-2000.

(2) *The conceptualization of health and health care*

The conceptualization of health and health care is undergoing revolutionary change. The World Health Organization has succinctly defined health as "a state of complete physical, mental and social well-being and not merely the absence of disease." The American Medical Association recently defined health as "a state of physical and mental well-being." Both definitions represent a significant departure from the past. The WHO definition has received wide acceptance. It has become the basis of a new national and worldwide cultural and social approach to health. The committee believes it may be assumed that it will be generally accepted by 1980-2000.

The idea that health is a state of well-being and not merely the absence of disease raises many new problems. For example, the distinction between medical care and health care is by no means clear, nor is the distinction between health care and all of what it takes to create, maintain or restore a state of complete physical, mental and social well-being. It is quickly seen that many of the most important causes of ill health have little or nothing to do with medical care or the lack of it, yet the diagnosis, treatment and prevention of ill health, no matter what the cause, are always proper concerns of physicians and the medical profession. Thus medical care and health care can never be entirely separated although they are by no means the same.

Some of the cultural and social components of ill health and need for health care services are easily identified. Inadequate nutrition, poor housing, poor working conditions, environmental pollution, poverty, inadequate education, inadequate use of genetic counseling, racism, personal and cultural attitudes toward smoking, abuse of alcohol and drugs, sexual promiscuity, abortion or sterilization more or less on demand, and a surprisingly passive acceptance of an enormous number of deaths and injuries on the highways and elsewhere, are among the many examples which can be cited of socially engendered needs for costly health care services. And the record

shows that physicians have been professionally concerned with reducing many if not most of these causes of ill health.

Question arose within the committee as to whether or not there might actually be a biological basis for physical, mental and social well-being and a biological cause for some social problems related to education, employment, health and welfare which will have to be identified and corrected before many social and health problems can be overcome. The committee could not answer this, but noted that the concept that human society is in fact a biological society is gaining ground in the growing recognition of the interdependence of healthy humans with a healthy environment. The recent emphasis on environmental and human ecology seems to be running deeper than the usual fad, and it is entirely possible that the latter part of this century will see the biological nature of human society given the same cultural recognition that the biological nature of man himself received in the late 19th century. If this takes place, as well it may, then health science will become one with physical, social and behavioral science; health care will become more obviously an expression of individual and societal behavior; there will be a more biological approach to many social problems; and the professional role of the physician as health scientist and health advisor will be given new definition in the complicated area of social biology.

(3) *On defining the scope of medicine*

The "Scope and Responsibility of Medicine" with respect to changing concepts of health and health care was the subject of a national forum conducted in *California Medicine* in 1968.¹ A wide variety of views were expressed. The problem was touched upon again in another forum, "Relevance Today and Tomorrow in Medical Education," published in 1970.² These discussions identified significant new dimensions to the traditional responsibilities of medicine, and to a certain extent spelled out a continuum of responsibility in personal, community, environmental and genetic or species health care, but did not define the precise role to be played by the physician in any of these categories.

¹Morrison JG, Knowles JH, Cashman JW, et al: The scope and responsibility of medicine—A forum with a purpose. *Calif Med* 108: 405-411, June 1968

²Watts MSM: Relevance in medical education—Some thoughts from a forum. *Calif Med* 112:47-52, June 1970

There is good evidence that the "new generation" of physicians is particularly aware of the new meaning and new dimensions in health care, of the new scope of medicine, and of many of the problems to be solved. Its members appear fully determined during their time in practice to move toward a closer realization of health as a "state of complete physical, mental and social well-being" for all. The impact of all this upon the physician and his practice by 1980-2000 will indeed be very considerable, particularly since the practice of medicine is likely to be far more health-oriented than disease-oriented by that time.

B. *Logistical Forces*

(1) *Population growth and change*

The increasing numbers of people in various categories who will expect and require health care services by 1980-2000 will place considerably greater logistical pressure upon health care delivery. There are various estimates of what will be the extent of population growth itself but it seems reasonable to expect that by the end of this century the population of the world is likely to have again doubled although zero population growth may have been approached in the United States and elsewhere. Greater longevity, with its accompanying incidence of chronic illness, also adds significantly to needs for health care services as the numbers in the older age groups become larger. There will be rising expectations, even demands, for better living and better health not only in California and the United States, but throughout the world. It may be anticipated that health and health care for all inhabitants of the globe will become not only a national but a "one-world" proposition. And along with the increase in numbers and expectations of people everywhere there will be much more mobility for many more persons while at the same time the size of "immobile minorities," such as the very young, the aged, the disabled, the poor or the mentally ill, is also likely to increase. All of this suggests that by 1980-2000 the national and worldwide logistical demands for health care services will necessitate new approaches to the delivery of health care services on the part of physicians everywhere, and it may be expected that the "haves" will somehow be giving more assistance to the "have nots" than is now the case.

(2) *Technologic growth*

Progress in medical science and in the technology of health care will also exert enormous and compelling logistical pressures. It has been stated that the body of medical knowledge has doubled each decade since the turn of the century. If this rate of progress continues until the year 2000, the amount that is known, and therefore to be learned and applied by physicians and other providers of health care services, will be at least four times what it is today.

This will have a number of important and predictable effects. Experience clearly shows that, as medical science and technology progress, there results wider and more frequent use of a greater number of more sophisticated services in the care, treatment, prevention or early detection of any given medical condition. This has been and will continue to be a primary cause of both rising prices and rising costs. Experience also shows that to the extent there is oversell of new progress and new technology the demands for new services may far exceed what is justified, with resulting overuse of scarce and costly resources. And when significant scientific or technologic breakthroughs occur, for example, as when poliomyelitis was conquered, or if cancer were to become an easily and inexpensively preventable disease, enormous changes occur in priorities and allocations for research, facilities, manpower and even in the composition of society itself, with resulting changes in the need for health care services which are not now predictable.

Scientific and technologic growth in health science will inevitably continue and will equally inevitably be a force with enormous yet quite unpredictable impact upon the logistics of the physician and his practice 1980-2000.

(3) *Logistical trends affecting resources*

The committee believes that a number of trends affecting resources for the delivery of health care services can be identified which will be important determinants of the internal logistics of the health care industry and of what the physician will be doing in his practice 1980-2000, although this subject needs much more scientific study than it has so far been given.

First and most importantly, the recent continuing growth in the percentage of the gross na-

tional product expended for health care must taper off and then stabilize at some level. This seems more likely to occur sooner than later, and the logistical impact of this is simply that finite resources will somehow have to come more directly to grips with infinite expectations and demands.

Second, the traditional work ethic of physicians and other health professionals appears to be changing. Many practicing physicians have started to seek alternatives to a work week of seventy or more hours and to avoid or leave situations where this is demanded. The trend is toward reduction in hours, more salaried positions and greater assurance of fringe benefits. Intern and resident physicians have applied pressures to improve their pay and working conditions with great success across the nation. And in contrast to previous generations many medical students today are not committed to the seventy-hour work week and many of them consider the practice of medicine as likely to be only a part of their life's work. There is ample evidence that other health professionals and health care workers are also seeking to improve their working conditions, pay and benefits. The elimination of charity for patients and the ending of exploitation of health care workers at all levels is not only proving costly but also reduces productivity, and this has and will continue to have considerable logistical impact on health care delivery.

Third, the demands for more and more goods and services are nothing new in our society, and the logistical response of the providers, business and industry has been to automate what can efficiently be automated and to program what can be effectively programmed, and where possible to eliminate the wasteful use of costly resources, particularly personnel. It is reasonable to expect that the growing national and worldwide aspirations for better health and better living will necessitate automated and computerized patient data banks, population and pollution data systems, and various kinds of monitoring or early warning signals, not only in patient care but in many aspects of community and public health. It may be expected that by 1980-2000 the physician, his practice and his patients will be closely linked to such automated systems.

Fourth, the logistical trends which have been described will give rise to much greater empha-

sis on a team approach to personal, community, environmental and species health care. This will require more involvement of physicians with other professionals and with the community, and more of the physician's time will be devoted to this and to such things as growing public demands for evidence of his continuing education and the demands of the delivery system upon him in terms of paper work, peer review and defensive medicine. Physicians will have less time to spend with their patients in the traditional relationships.

These logistical trends all suggest that an important disparity between supply and demand for health care services is going to persist and that it will dominate health care delivery, the health care industry and the physician and his practice in 1980-2000. The bargaining position of physicians, both individually and collectively, will continue to be favorable and the number of options for paid professional services will increase. However, if the work force of physicians of high caliber in practice is to be maintained, the incentives for practice will have to be maintained at a satisfactory level by society.

C. *Ethical Forces*

The need to reassess values and ethics in health care is an inescapable corollary of the conceptual and logistical forces just discussed. In fact it is quite evident that medical ethics have already begun to change in response to the power of these forces. For example, there has just recently been an almost complete turnabout in the ethics of human abortion which would have been undreamed of only a few years ago. And clearly this is only a forerunner of what lies ahead. New technology in such fields as organ transplantation, genetic engineering, sex selection and embryo culture, for examples, have begun to give rise to hitherto unimagined conceptual, logistical and ethical problems which will be far-reaching indeed. The new emphasis upon ecology and the quality of life and of the environment which supports it adds yet another dimension. And since health care services, whether for persons, for the population as a whole, for the species, or for the environment, will always be insufficient for the foreseeable future in both quality and quantity to fulfill the expectations, value choices involving ethical considerations will have to be made. This will surely require

reexamination of many present-day assumptions and attitudes, not only in medicine, but also by society as a whole.

It is suggested that most, if not all, of the new ethical issues which are either here or on the horizon and which will particularly concern physicians can be reduced to the terms of a conflict between a traditional reverence for each and every human life until death can no longer be thwarted, and a newer reverence for the health and well-being of society and humanity as a whole which is now assuming increasing and even compelling importance as a condition of quality of living for the human species. The first is the historical ethic of the physician and the second may become the historical ethic of society. However this may be, whenever the health interests, well-being or fulfillment of society as a whole becomes pitted against the health interests, well-being or fulfillment of the individual who is a patient, questions of values and ethics are certain to arise and physicians are certain to be involved. Although physicians' ethics and attitudes ultimately will adapt to reflect those of the society, since the law will tell the physician what he may and may not do, it is also true that physicians' knowledge and expertise in the subject matter of health and ill health can and should influence the ethical and value systems as these are developed by society.

The mind boggles at the kinds of issues which will have to be faced and resolved even as soon as 1980-2000. Practicing physicians will be particularly concerned when choices must be made in very personal situations, as in the very central question of life and death, or when decisions are to be made as to who among those who could benefit is to receive some costly treatment drawing disproportionately upon limited health care resources. As the need for such value decisions increases, it seems inevitable that medicine and society will establish new principles or criteria upon which to base them. Indeed this has already begun. As an example, the principle of physiologic "unviability" has now appeared upon the scene. It is quite generally accepted to justify interruption of life support in certain circumstances at one end of the life span, and its extension is now being discussed in terms of justifying interruptions of life support in certain circumstances at the other. Where a decision is to be made as to who is to receive a costly treat-

ment which cannot be made available to all who might benefit, again both medicine and society have begun to experiment with sharing this kind of decision on an individual case basis, as was done in the early years of the artificial kidney. It was suggested in the committee discussions that some kind of a court may eventually be needed to make the more difficult decisions.

In less personal situations in health care the ethical conflict will still be found. For example, in the overall distribution of national resources for research, education or services in health care, there is the question of how much should be assigned to the tangible and immediate personal needs of the present, and how much to the more intangible but nevertheless readily recognized needs for the health and well-being of society in the future.

The committee believes that all of these ethical, philosophical and practical issues, however they may be resolved in an ever-changing health care situation, will constitute important forces affecting the physician and his practice 1980-2000. Physicians will be deeply involved in carrying out the ethical and value decisions of society and should also be deeply involved both as citizens and professionals in their formulation. The committee commends the House of Delegates of the California Medical Association for its 1971 decision to establish the Committee on Continuing Study of Evolving Trends in Society Affecting Life, the first in any medical society to address itself to a study of these important ethical forces as they will surely influence medical practice in profound ways which cannot now be entirely foreseen.

D. Regulatory Forces

The conceptual, logistical, and ethical forces or imperatives which have been discussed can produce chaos in health care, as some say they already have, unless controls or regulatory forces are introduced. Since society has the ultimate responsibility and has determined that access to health care of high quality at reasonable cost is the right of everyone, society will sooner or later have to assume the authority to exercise its responsibility. This became inevitable as soon as health care became something worth having and was decreed to be essential by society. The process of developing these necessary controls is already under way. The part physicians will play

in this is not yet entirely clear, but just as medicine could not assume *all* responsibility for health care, it is unlikely that society through government can do so either, without far closer collaboration with physicians and with far more of their professional help than has so far been sought. It is quite likely that by 1980-2000 this will have become recognized and that medicine will play a far more significant role than it now does in the regulation and control of health care.

Regulation of scientific or technologic quality of facilities, equipment, drugs and services is already well started and is being carried on under both governmental and professional auspices. Internal professional controls such as accreditation, peer review, certification, and discipline of members by professional organizations, all of which are already increasingly subject to emasculation through court review, may not prove to be strong enough to accomplish what is needed. It is likely that professional controls will sooner or later be strengthened, perhaps through some kind of review of professional reviews or some modification of such models for regulation and control as are now applied to farmers, labor, or various public utilities. Regulation of access to care, of how the egalitarian principle is to be applied, of when health care should be made compulsory in the overall interest of society, as is now the case with persons who have tuberculosis or leprosy, and of when and under what circumstances persons may be selected to receive certain special or unusual services, may all be expected to develop. Closer regulation of costs is essential. More accurate determinations of value received and better cost effectiveness data are badly needed, but the means to develop these data are as yet not available, and until they are, crude economic controls will be applied to restrict the number of services rendered and contain their costs in a more or less ruthless and arbitrary fashion.

Political solutions to many problems in health care are inevitable and will themselves constitute regulatory forces which will affect the physician and his practice in 1980-2000. It is noteworthy that many, if not most, of the attempts at political solutions so far have only compounded the problems they were intended to solve, and have often proved counter-productive. The delusion and illusion that all health care problems are political and therefore capable of political solu-

tion is at present both widespread and dangerous since the evidence so far is that politicians have yet to demonstrate much expertise in this field. However, there are some early indications of a beginning political recognition that health care may be something like a china shop, and not likely to serve its customers either efficiently or effectively in the presence of a bull which pays little heed or attention to the desires of either the providers or customers or to the delicate and sensitive nature of the wares to be distributed from the shop. It is to be hoped that this recognition will come before there has been too much destruction in the shop of health care delivery.

The conceptual, logistical, ethical and regulatory forces discussed in this section are not to be denied. They are realities which both medicine and society must learn to understand and to which they must adapt. They will profoundly influence both medicine and the "practice situation" by 1980-2000.

III. Problems to be Solved in the 1970's

The committee believes the 1970's will be a period of experiment and change when solutions will be sought for many of the unsolved problems in health care. This will be a time of flexibility, fluidity and flux during which the patterns for the future can be molded and shaped. A more stable and possibly quite different system of providing health care services may be expected by 1980-2000.

Just as events of the past have led up to the present, the present will lead to the future. Three quotations seem to aptly summarize the situation as we find it today. In 1969 David E. Rogers, M.D., of Baltimore said:

First, as doctors we are privileged to be citizens of the wealthiest, most technologically advanced nation in the world.

Secondly, since the early 1900's we have developed the best system for training skilled physicians to be found in modern society. We attract some of the very best young minds into our profession. We have evolved an educational system that turns out individuals with fine biomedical science backgrounds and greater clinical skills than anyone would have imagined possible at the turn of the century.

Third, since World War II we have developed biomedical research programs that have made

more contributions to fundamental and applicable biomedical knowledge than were made in all previous medical history. These new insights have permitted a dramatic change in what we can do for our sick patients.

Lastly, as physicians we now find ourselves the unwitting and rather surprised captains of the fastest growing industry in this country—the health care industry. Last year health care expenses consumed over 6 percent of the gross national product, an almost incredible \$54 billion!³

In 1970, William L. Kissick, M.D., of Philadelphia, published the following statement:

The health endeavor in the United States, a \$60,000,000,000 human services enterprise, is in a state of crisis that challenges the continuation of its pluralistic, independent, voluntary nature. Health care, although still predominantly a private-sector activity, is no longer solely the private concern of the individual. The evolution of the role of government has proceeded through four phases, beginning with the categorical grants-in-aid (1935), investments in the development of health resources (1946), organization and delivery of health services (1963) and a transition into comprehensive health care system (1967). Health policy deliberations during the 1970's, including debates over National Health Insurance, must focus on the modification of financing mechanisms and patterns of organization if society is to realize the most effective utilization of its health resources to provide health care for a population projected to reach 250,000,000 by the end of the decade.⁴

In 1971, Robert H. Ebert, M.D., of Boston, wrote the following:

What is of interest is that the manner in which medicine is practiced has followed the technology rather than the other way around. Very little attention has been paid to the question, "What organization of medical services would be most convenient for the patient and the community, and how can technology solve the problem?"⁵

The committee now addresses itself to what it perceives as some of the very most basic problems which it believes will somehow be solved during this decade.

³Rogers DE: Some reflections on medicine today and tomorrow. *Am Int Med* 70:853, April 1969

⁴Kissick WL: Health policy directions for the 1970's. *New Eng J Med* 282:1343, June 11, 1970

⁵Ebert RH: A note on the impact of technology on the practice of medicine. *Technology Review* 72:49, April 1970

A. Definition of Terms

A necessary prerequisite for a more rational or scientific approach to fulfilling the national commitment of health care for all will be to develop better descriptions or definitions for many of the terms in common use. For example, until there is more general agreement with respect to exactly what "medical care" or "health care" consists of, or the scope and content of "comprehensive health services," or precisely what is meant by such terms as "equal access," "quality assurance" or "cost benefit" and how these are to be measured, it will continue to be difficult to determine either exactly what needs to be done or what has been accomplished. Even the word "consumer" lacks definition. Sometimes this refers to the patient who receives the services, sometimes to whoever purchases or pays for the services, and sometimes even to the medical practitioner who decides which new products, procedures or systems of health care he will use or "consume" for his patients.⁶ Agreement on definitions of terms is an essential first step in the development of any science, and more agreement in the semantics of health care is essential and may be expected as this new science of health care begins to take shape in the 1970's.

B. Anatomy of Health Care

As a corollary to better definitions and descriptions of terms there will be needed a better identification of the many elements of health care and their relationships with one another. For example, what are or what ought to be the roles of the primary physician, the physician specialist, the nurse practitioner, the pharmacist, and the host of allied health personnel? What can automation, data storage and retrieval, or computer assisted services do and how can they wisely be used in health care? What are the most appropriate uses of resources and services of various kinds for prevention, health maintenance, care for the sick, care for the not sick but scared, or for "defensive medicine" in behalf of both provider and consumer? Which services are better centralized, which should be decentralized and how should centralized and decentralized services be linked? When should the care be at home, when in a physician's office or

clinic, or in a health center or a hospital, or in a highly specialized regional center? These are problems in the identification of the parts of health care and their relationships to one another. There will be experiment, and considerable experience with these relationships surely will be gained during the 1970's.

C. Quality, Costs and Financing

Quality and costs in health care are already causing great concern. No truly satisfactory means have yet been found either to assure quality or to control costs. Financing, now largely by private or governmental third parties, is rapidly falling behind in its race with rising costs, and this is giving rise to an absolute necessity for cost containment even if this be at the expense of quality and consumer and provider satisfaction. Social causes of illness and injury have yet to be clearly identified and recognized for the important and so far almost completely overlooked role they play in generating health care costs; and many basic social and biologic questions of "viability" and "unviability" and "quality of life" which contribute enormously to health care costs have yet to be faced. The 1970's will surely be a period of struggles and turbulence as unlimited demands, unresolved social problems, rising costs and increasingly complex services of higher quality compete with other needs for funds and resources.

D. Governance of Health Care

The 1970's will also be a period during which there will be trial and experiment with the governance of health care, and the necessary regulatory forces in health care will be further developed and refined. It is not yet clear just how the regulatory forces should be applied or how the governance should best be done. Experience to date shows that attempts at governance without involvement of providers, and this includes physicians, and consumers in both the planning and governing processes have been conspicuously unsuccessful. It may be anticipated that some new models for the governance of health care will be developed during the 1970's and that what is needed will vary in different situations. Regulation and governance of health care can be developed primarily in either the private or public sector, and the control of health care

⁶Bennett JL: Conditions and problems of technological innovation in medicine. *Technology Review* 72:43, April 1970

can also be primarily in either. A task for the 1970's will be to determine how all this will be accomplished.

E. *A Decade of Experiment and Change*

It is safe to predict that the 1970's will be a period of challenge and change in health care. Trial and experiment and the assembling and disassembling of health care delivery systems will be the order of the day, and out of all this will emerge the pattern or patterns of health care which will probably persist at least until the end of this century. The 1970's will be a decade of experiment and change during which what is to come will begin to take shape.

IV. Some Predictions for 1980-2000

The committee believes that it is already possible to offer certain predictions with respect to what health care in this nation will be like in 1980-2000. The forecast can only be in generalities and is necessarily incomplete.

A. *Financing*

It is expected that by 1980 costs will be of less concern to the person who is sick. There will no longer be any significant financial deterrents to personal health care whether for prevention, health maintenance, crisis care or for needed rehabilitation. Some kind of universal health insurance will be in full operation and it is likely that there will be options from which to choose. For many reasons co-insurance factors will be involved in any financing mechanism. Considerably more sophisticated consumer and provider participation in both planning and programming will have been achieved.

B. *Better Defined Services*

The problems of financing will have resulted in more precise definitions of what it is that is being bought or paid for in terms of personal health care, health maintenance or preventive care, community health care, and environmental or species health care. The need to have some measure of value received for dollars spent and to assess the cost benefits to be anticipated from the investment of health care resources will bring this about. There will be a clearer understanding of just what the health care is that society has determined to be the right of every-

one, and there will be a more realistic appraisal of just what its benefits are likely to be for the individual and for society. The variety of services to be rendered by physicians throughout the spectrum of health care will have been better recognized, defined, and probably valued; and means will have been developed for providing compensation for these services.

C. *Physicians as Managers*

By 1980-2000 it will almost certainly have been learned that the managerial role of the physician cannot any longer either be by-passed by health care planners or ignored by physicians since the practicing physician in any system of health care is and will continue to be the key decision-maker in the use of services, equipment and facilities. This critical decision-making function in actual day-to-day practice necessitates physician involvement in many managerial functions such as planning, development of services, cost control, quality assurance (including over- and under-utilization of services), and even operations. As health care delivery systems become increasingly complex—and they inevitably will—the managerial role of physicians will become correspondingly more important and more widely recognized. Management skills will be needed by physicians together with a greater understanding of the organizational dynamics of working with other autonomous professionals in team operations. This is already well under way. New professional skills are being developed which will become formalized. By 1980-2000 physicians will be far more effective participants in the management and operation of health care programs and systems than is the case today.

D. *Automation and Programmed Health Care Services*

Automation and programmed services of various kinds will play a prominent role in health care in 1980-2000. There is general agreement that computer banks will be used to store patient care data for both mobile and immobile populations. The information will be available on an on-line basis with telephone access from doctor's office, hospital or patient's bedside. Disease detection and diagnosis will be aided by such things as automated screening systems, computer assisted histories, paramedical physical examinations, multiphasic autoanalysis, implanted

monitors of body systems, readily available telemetry of various kinds and computer assisted diagnosis; and much in the way of prevention and health maintenance will be carried out by non-physicians. Since all of this will necessarily be under the supervision of physicians and used by physicians, considerable technical knowledge in these fields will be required of the practicing profession. Automated and programmed assistance will be expected to free the physician's time and extend his reach, and thus enable the profession to provide more services to more people. Whether personalization of health care will improve or deteriorate under these conditions of practice remains to be seen.

E. *Personalization in Health Care*

The committee believes that personalization in health care can and will be retained and strengthened in the face of much more complexity and systematization in health care. Many educational, cultural and language barriers will need to be overcome. More physician time will be freed for this purpose by automation of what can be automated, and systematization of what can be systematized. Greater use will be made of specially trained personnel who will extend the reach of the physician in a very personal way and help to bridge language, cultural and even distance gaps between the physician, mainstream medicine and the persons to be served. The wave of the future seems actually to be toward more personalization in medical practice. A thoughtful spokesman for younger physicians notes that impersonal or "dehumanized" services, no matter how "efficient," are in large part what bothers young Americans today. Halberstam⁷ further states:

Many authorities criticize American medicine for being under-organized and inefficient. Their proposed solutions involve varying degrees of industrialization and larger groups of physicians practicing together. A central malaise in American life today, however, is depersonalization, and the radical analysis of our society calls for smaller, less rigid units of service. In the long run these may be more efficient than larger units planned by the cost accounting method. Medical care, being a personal service, may develop dis-economies of scale early on. Any reform of American medicine

must be based not only on the need to get care to all people, but also on growing demand of all citizens, especially the young, for personal humanistic services.

It seems more than likely that personalization of services will somehow survive and even thrive within the complexification of health care which will occur in 1980-2000.

F. *The Delivery System*

There will be no universal delivery system. The nation is too diverse culturally, geographically and philosophically for this to be acceptable or to succeed. Rather the "system" will be pluralistic and there will be options for providers (including physicians) and for consumers (including patients). Services will be rendered in the least expensive setting which will assure quality and satisfaction. There will be greater emphasis on home care, ambulatory care, and avoidance of expensive institutionalization. More complex services will be centralized to the extent necessary to assure quality and efficiency. The trend toward group practice will continue. Means will be found within the pluralistic system to link those services which are best centralized or regionalized with those which must remain decentralized for personalization and consumers' convenience. Government, labor management health trusts, and other funding agencies will use their financial "leverage" to encourage whatever kinds of delivery systems they happen to favor at the moment. It is likely, however, that the need to offer programs that are satisfactory to both the consumers and the providers of health care will loom much larger than is the case today.

G. *Freedom of Choice*

There will be generally less freedom of choice for both the doctor and the patient, although new options will have become available to many persons now outside the mainstream of health care. There will be more controls of uses and abuses of day-to-day health care services. Since the demand, especially for certain complex or expensive services, may exceed the supply, it is possible that in certain situations the law or the courts, rather than physicians, will decide who is to receive what of these services. All of this will be an inescapable result of the need to use avail-

⁷Halberstam MJ: Liberal thought, radical theory and medical practice. *New Eng J Med* 284:1180, May 27, 1971

able resources as efficiently as possible, and it will tend to reduce rather than increase the degree of freedom of choice for both doctor and patient. Conflicts will occur when the interests of patients run contrary to the rules and priorities of the regulatory bodies.

H. *A Science of Health Care*

When the present babel of terms can no longer be tolerated, the science of health care delivery will enter the descriptive phase which is the first step for any science. This may be expected to occur soon. When this has been done and the anatomy of health care is better described and defined, then it will be possible to develop the relationships between the technological, social, economic and political components of health care in a more scientific fashion. The science of health care delivery will have come into being. As more understanding is achieved on a scientific basis, more accurate predictions and corrections can be made and disruptive or destructive upheavals will less likely come about within the pluralistic health care system. All this should be well under way in 1980-2000, but since health care will always be changing even while it is being examined, it is worth noting that the science to be developed will be less precise than the mathematical or physical sciences and will have more of the characteristics of a biological science. Its accuracy will also be dependent upon further basic advances in the social and behavioral sciences. Many decisions in health care will therefore probably have to be made without a sufficient base of knowledge for quite a while to come, much as is done in clinical situations in patient care when decisions have to be made when full information is not available.

V. *The Role of the Physician in Health Care*

As the committee examined the powerful determinants which will shape health care for 1980-2000, the problems to be solved in the 1970's, and its predictions for 1980-2000, it sought to identify those functions which are peculiar to the physician and which therefore will define or describe what his essential role will be in health care. This problem is approached from a standpoint of (1) some fundamental relationships of physicians with others,

(2) the scope of medicine and health care, and (3) the essential professional functions of the physician.

A. *Some Fundamental Relationships*

(1) *With patients*

The physician-patient relationship will always be at the heart of patient care, yet in many ways it must change and is changing. For one thing the physician is no longer in the leading role, if indeed he ever was. It is the patient who decides when and if he will seek care, except in crisis situations. If he is conscious, he must give his "informed consent" to whatever is done. And every physician knows he may or may not carry out whatever treatment is "ordered." Yet there is a deep and persisting sense of need on the part of both physician and patient for some kind of close personal relationship, particularly in times of illness and stress. The difficulties of maintaining this traditional and personal one-to-one relationship will increase. The rise of group practice, third party payments for services, peer review, and increasing government intervention with varying degrees of interest in quality and cost control have all but demolished the personal and confidential nature of this relationship. Also, there simply are not, nor can there ever be, enough primary or family physicians to provide modern comprehensive care in this traditional one-to-one doctor-patient relationship equally to all. And furthermore, as greater access to more health care services becomes available to more persons, it is clearly evident that there are significant language, education, distance and lifestyle barriers to these one-to-one relationships between physicians and many patients. But the doctor-patient relationship must somehow be retained and physicians must somehow overcome these many barriers, and continue as competent and trusted advisors to patients.

(2) *With society*

Society plays the lead role in medical and health care, not physicians. Society licenses physicians to practice medicine and the law prescribes what they can and cannot do. The courts hold physicians responsible for their actions in accordance with society's, and not the physician's, interpretation of the law. Society decides how much of its overall resources it will allocate

to medical and health care and to a considerable extent how this will be divided for support of research, for education and for patient care. In the long run the practice of medicine will inevitably reflect the social philosophy of the day. For example, if society is free enterprise, medicine will be free enterprise; if it is liberal or socialist, this will affect medical practice; or if the "new generation" takes over, Reich's Consciousness III American will no doubt dominate the philosophy of medicine as well as of society.⁸ Medicine has much expertise to offer for the betterment of a health- and ecologically-oriented society. The profession's responsibilities are not only to patients, but to society as well. By 1980-2000 this latter professional responsibility will require physicians and organized medicine to develop technologic, social, economic and political skills which they do not now have. Some of these have been discussed in the Fourth and Fifth Progress Reports of this committee.

(3) *With health care delivery systems*

Health care delivery systems are now an integral part of patient care and the health care of the public. Just as the physician has always considered the social and economic circumstances of his patient, so he must now, and for the same reasons, begin to consider the social and economic circumstances of the delivery system within which the patient is receiving his care. Since it is the physician who determines what care is needed and with the consent of the patient orders that it be carried out, it is he who determines to a large extent what costs are to be incurred. It is only logical and appropriate that the physician should now extend his concern for the social and economic circumstances to the health care plan under which the patient is receiving his treatment. This has begun to occur. Physicians are becoming more directly involved in utilization control and peer review to protect quality and to control costs in delivery systems. Also, there are signs of greater participation by physicians in the planning and operation of health care plans. Not only consumers, but providers and particularly physicians, must be in-

volved in the development and operation of health care programs if they are to be satisfactory to both consumers and providers, and this is necessary if they are to work well. It seems safe to assume that by 1980-2000 physician participation in health care delivery systems will include many more managerial functions and organizational services and procedures than is the case today, and that provider and consumer satisfaction will have come to be considered as essential as are quality assurance and cost effectiveness for a successful health care plan.

(4) *With other health manpower*

Specialization throughout the health manpower field is undergoing important growth as a result of a rapidly increasing complexity in both the scientific and social aspects of medical and health care. Many physician specialists now restrict their practice so sharply that they really have become highly skilled technologists, while many non-physician technologists or other health care personnel aspire to, or have achieved, a professional status which they believe now entitles them to play an active role in planning and decision making, not only for health care in general, but for individual patient care as well. While physicians pride themselves on their technologic role in patient care, the fact is that non-physician health personnel can be trained to perform almost any technological function that can be performed by a physician. All of this has begun to produce a bewildering confusion in the structure and organization of health manpower, and much that was formerly done only by physicians is now being done by others.

There is very real danger that this process of fractionation will lead to multiple standards in medical care as more authority and more responsibility is given to persons with different levels of competence and training. The current trend toward separate licensure for many health related professionals, many or all of which are striving to assume both managerial and technological functions in health care is likely to bring this about. The committee believes that more attention should now be given to developing an appropriate health manpower structure which would better relate the functions of the various health professionals to one another, thus encouraging a single level of high quality patient care and at the same time fostering more upward

⁸ As stated in a *California Medicine* editorial, Consciousness III American is described as: "... 'the new generation' which seeks liberation from the imperatives of society, sees through 'phoniness' with astonishing clarity, is deeply committed to personal fulfillment for all as well as to the betterment of communities and of society as a whole, and which seeks to share actively in the decision-making processes through what is coming to be called 'participatory democracy.' " (Watts MSM: Of pharmacists, physicians and health care. Calif Med 114:84, May 1971)

and lateral mobility for health personnel so that persons in the health manpower field will have a greater opportunity to upgrade or change their roles than is available to them today. As such a health manpower structure develops, physicians may need to give more attention to their managerial functions in health care than is now the case, and delegate more of their technologic functions to highly specialized physicians, who will become increasingly recognized as skilled technologists rather than as physicians, and to other technological professions and personnel. This managerial function may well prove to be essential if the physician is to continue to play his professional role.

B. *The Scope of Medicine and Health Care*

A review of the discussions summarized in the earlier sections of this report suggests that medicine and health care are beginning to take on substantially new dimensions. The general recognition of health care as a right, the shift to the positive concept of health as a state of well-being, and the growing realization that health is soon to be a one-world proposition within the framework of a closed population and environmental ecosystem are already bringing about changes in the activities of physicians which can only loom larger by 1980-2000. The committee suggests that the scope of medicine, and therefore the scope of the physician's involvement, now encompasses the following:

- (1) *Care of sick, injured and emotionally disturbed persons.*
(This includes traditional diagnosis and treatment, relief of suffering, restoration of function and rehabilitation of individual patients.)
- (2) *Health care of persons not ill.*
(This includes prevention of illness, injury and emotional disturbance and much of what is now being called health maintenance.)
- (3) *Health care delivery systems.*
(This includes access to health care; the quantity, quality and availability of services, cost control, efficiency, effectiveness, cost benefits, etc.)

(4) *Community health care.*

(This includes attention to the social causes of ill health such as poverty, housing, sanitation, education, cultural behavior, transportation barriers, etc.)

(5) *Environmental health care.*

(This includes attention to health in the closed ecosystem; pollution of air, land and water; misuse, overuse or exhaustion of resources essential to health, well-being or life support; and the overall quality of the environment.)

(6) *Genetic or species health care.*

(This includes attention to the health of the human species as such, including genetic counseling, and other means of improving the health of the human race.)

Physicians have already become involved throughout this whole spectrum of health care, and this involvement can only increase. It may be expected to occupy most if not virtually all of the composite physician's time by 1980-2000.

C. *The Essential Functions of Physicians*

Since consumers, patients, society, other professionals, and health care delivery systems will play larger and more important roles in the delivery of medical services and health care, and since the new scope of medicine and health care will become more widely recognized by 1980-2000, it is now necessary to identify exactly what are the professional functions which physicians and only physicians can perform. This question is more easily asked than answered, yet it must be answered if there is to be a base upon which to construct a logical projection of what the composite physician will be doing in 1980-2000.

The committee believes that it is able to identify three professional functions of the physician which can be performed only by physicians, and which taken together in fact define what the physician does throughout the spectrum of health care. These three essential functions are as follows:

- (1) *The physician gives a professional opinion or judgment based upon his knowledge, experience and expertise with respect to health and its derangements.*

- (2) *The physician is an essential participant in all the decision-making processes throughout the whole spectrum of health care because of knowledge of health and its derangements, and of health care.*
- (3) *The physician performs certain professional procedures and services in health care, and plays certain roles for which he must have practice skills.*

It will be quickly noted that each of these three essential professional functions derives from the physician's knowledge and professional competence with respect to health and its derangements. Medicine is the only authoritative profession for this. Conversely, without professional knowledge and professional competence with respect to health and disease, injury and emotional disability in humans, the physician cannot perform his essential functions throughout the spectrum of health care. Lacking this broad competence and expertise the physician can only become some kind of a specialized technician qualified to perform only a specialized technological function in the rendering of medical or health care.

(1) *The professional opinion*

The professional opinion or judgment of the physician is based upon his knowledge, experience and expertise as to

- what is wrong?
- what is probably going to happen?
- what can be done about it?

as this relates to how health is or may become impaired. A physician, and only a physician, can give this sort of professional opinion authoritatively, since health and its derangements are his special area of competence. The committee believes this is the most basic service rendered by physicians, and that it can be rendered throughout the spectrum of health care only by physicians.

(2) *An essential participant in decision making*

The function of the physician as an essential participant in the decision-making processes throughout the whole spectrum of health care is a new concept. It appears to be valid. Physicians only occasionally make decisions alone.

Nearly always this is done in collaboration with patients, families, other physicians, other professionals or society. However, when physicians are left out of the decision-making processes in health care at whatever level, difficulties are apt to occur. This is self-evident in patient care, but evidence is accumulating in other categories of health care to show that unless physicians participate effectively in the decision making the result is likely to be a program or plan that is ineffective, unworkable, or unduly costly for the results achieved. Just as patients and consumers are essential in health care planning and operations, so are physicians. So far neither the profession nor the public has fully recognized this. Yet the need for physician participation in decision making is clearly present. "What is wrong?" and "what is probably going to happen?" and "what can be done about it?" as they relate to how health is or may be impaired extends all the way across the health care spectrum, and the physician as the authority on health and its derangements has an essential contribution to make to these decision processes. It is reasonable to expect that by 1980-2000 physicians will play a much larger role in the decision-making processes in health care, although as is the case now, this will be shared with others throughout the spectrum. This will require much new knowledge and many more and different professional skills than most physicians possess today. And as physicians perform this essential function more often and with greater sophistication, better provision for compensation for this kind of professional service by physicians will be needed and will develop.

(3) *Essential services and essential roles*

The physician performs many essential procedures and services in health care, and these may be expected to increase in number and variety. It is a fact worth noting that the rendering of a professional opinion or judgment and participation in decision making are the only functions that the physician cannot delegate either in whole or in part. Many other essential procedures and services may be accomplished by the physician himself, or through the use of non-physician professionals with special training, or through means of automation of programmed technology. By 1980-2000 these essential procedures and services which the physician may

or may not perform himself will extend throughout the full scope of medicine and health care. Procedures and services in the care of the sick, injured and emotionally disturbed are quite familiar, as are those in the case of persons not ill. More recently physicians have begun to carry out procedures and services in utilization and peer review for health care plans. Ways will be found to compensate physicians when they perform these new services. This has already begun. Physicians are now beginning to be compensated for their services in utilization control and peer review. The committee is convinced that new procedures and services which may be performed by physicians can readily be anticipated in community, environmental and species health care.

Recognizing that the physician himself cannot and will not be carrying out all the procedures and services in health care in 1980-2000 even to the extent that he is doing this today, the committee now identifies certain practice skills which it believes physicians will need to possess or develop if they are to perform the essential functions which have been identified. These are as follows. In varying degrees the physician must be a:

- Problem solver
- Manager
- Skilled technician
- Teacher or advisor
- Advocate

These roles apply to each of the essential functions of the physician as these may be expected to develop throughout the whole spectrum of medical and health care. They are not new, nor are the kinds of practice skills they require. But considerable new knowledge and considerable refinement of these skills will be needed by physicians if they are to be competent to play these roles in the practice environment that may be anticipated for 1980-2000.

VI. The Practicing Physician— A Composite for 1980-2000

The concept of the "composite" physician as discussed herein embraces all physicians and indeed the whole corpus of the medical profession. When this concept and predictions for the practice of medicine are projected to 1980-2000, as this study attempts to do, it is clear that not

only will there be many more specialties or options for an individual physician's practice, but also the scope of medicine and medical practice of which the practicing physician and the profession as a whole should have a broad awareness will also have increased, and increased dramatically. The practice of medicine already embraces many specialties. Even today no one physician can claim competence in them all, yet every physician who practices is expected to have a broad awareness of the current capabilities and limitations of the branches of medicine other than his own in order to be able to advise his patients. This will still be true in 1980-2000 when physicians will still need such competence and awareness to perform their essential functions, not only for their patients but in many other aspects of medical and health care. The scope of this competence and broad awareness which should be shared by all practicing physicians and the whole corpus of the medical profession is conveniently considered in a "composite" for the practicing physician in 1980-2000.

Based upon what has been discussed earlier in this report, the practice situation as it may be anticipated for 1980-2000 is summarized in terms of the scope of medicine and the practice environment, and then some of the relationships of the essential functions of physicians to the various categories of health care are considered.

A. The Practice Situation—1980-2000

- (1) *The scope of medicine* will be very greatly expanded and will embrace the following as previously defined:
 - (a) Care of the sick, injured or emotionally disturbed
 - (b) Care of persons not ill
 - (c) Health care delivery systems
 - (d) Community health care
 - (e) Environmental health care
 - (f) Species health care
- (2) *The practice environment* will be one which is increasingly affected by the powerful determinants previously considered and the predictions for 1980-2000 previously discussed:
 - (a) Conceptual forces
 1. The right to health care
 2. The conceptualization of health and health care

3. The scope of medicine as defined above
- (b) Logistical forces
 1. Population growth and change
 2. Technologic growth
 3. Resource supply and demand
- (c) Ethical forces
- (d) Regulatory forces
- (e) Predictions for 1980-2000
 1. Financing
 2. Better defined services
 3. Physicians as managers
 4. Automation and programmed health care services
 5. Personalization in health care
 6. The delivery system
 7. Freedom of choice
 8. Science of health care
- (3) *The essential functions of the physician, which will be performed comprehensively by the "composite" physician and to a greater or lesser extent by all physicians and the profession as a whole throughout the scope of medical practice, are the following:*
 - (a) To render authoritative opinions concerning health with respect to
 1. What is wrong
 2. What is probably going to happen
 3. What can be done about it
 - (b) To participate in decision making at all levels of health care
 - (c) To perform procedures and services as
 1. Problem solver
 2. Manager
 3. Skilled technician
 4. Teacher or advisor
 5. Advocate

B. Medical Practice—1980-2000

With this view of the practice situation as it may be foreseen, the committee now envisions what it believes medical practice will be like in 1980-2000. There is no attempt here at detail or to be complete, but rather to paint a broad picture with broad strokes. The essential functions of the physician, as the committee has identified them in this report, are considered for each category in the scope of medicine and health care, as

the committee has defined these, and in light of the practice environment, as this has been discussed.

- (1) *Care of the sick, injured and emotionally disturbed (Table 1)*

TABLE 1.—Care of Sick, Injured and Emotionally Disturbed

(This includes traditional diagnosis and treatment, relief of suffering, restoration of function and rehabilitation of individual patients.)

Professional Opinion

When rendering a professional opinion or judgment with respect to a patient, the physician performs his most basic and fundamental service. To be authoritative this must be based upon knowledge of the nature of disease, injury or emotional disturbance as these relate to health, and upon a knowledge or awareness of what can be done to help the patient. This assumes a broad as well as often specialized background in the art and science of clinical medicine.

Participant in Decision Making

This occurs when the physician and the patient, his family, or a health team confer and agree upon a course of action to be followed in the care of a person who is sick, injured or emotionally disturbed. The decisions may be for medical, surgical, psychological or sociological treatment and it is necessary that the physician be aware of the resources for each which are available.

Procedures and Services

(Practice Skills)

(1) Problem Solver

Example: In the care of the sick, injured or emotionally disturbed persons the physician is usually the principle problem solver. He uses the familiar techniques of the history, physical examination, laboratory studies and consultation as needed. He evaluates the effectiveness of his problem solution by follow-up.

(2) Manager

Example: The physician is the prime mover and manager of complex problems in patient care, principal architect of the "game plan," and is concerned with the individuality of the "whole patient" and with preserving personalization and human dignity as the patient is "processed."

(3) Skilled Technician

Example: The physician performs specialized skilled technical services or procedures such as occur in surgery and other specialties including general or family practice.

(4) Teacher-Advisor

Example: Physicians serve as teachers and advisors to patients, their families and health teams in patient care. Their effectiveness depends upon their skills as teachers, their prestige and the trust and confidence they engender.

(5) Advocate

Example: The physician will be the advocate for the patient, especially where the patient's interest finds itself in conflict with pressures from the practice environment, or when the patient is having difficulty in achieving access to benefits or resources which he needs and to which he is entitled.

This is the traditional, primary and continuing responsibility of the physician. His basic competence here, as throughout the spectrum of health care, lies in his professional knowledge of health and its derangements, and of what can

TABLE 2.—Health Care of Persons Not Ill

(This includes prevention of illness, injury and emotional disturbance, and much of what is now called health maintenance.)

Professional Opinion

In the health care of persons not ill, the physician's professional opinion with respect to what constitutes health and what does not, what is wrong, what is probably going to happen, and what can be done about it, remains fundamental. To the extent this professional opinion is not sought or is ignored, waste and costly inefficiency in the care of persons not ill often occurs.

Participant in Decision Making

It is important that physicians participate in the decision making for health care of persons not ill, particularly where other than physicians will provide this care. This is essential in order that such programs will be of assured quality, be acceptable to and used by physicians, and be linked to the patient care delivery system to provide continuity of care should the "person not ill" be found to need definitive care. It will be necessary for physicians to have some understanding and competence with respect to these programs.

Procedures and Services

(Practice Skills)

(1) Problem Solver

Example: Problem solving in the care of persons not ill will include research into the cost effectiveness and cost benefits of those services and into the costly "myths" concerning prevention and health maintenance as well as dealing with the problem of any abnormality which may be discovered in the care of a "person not ill."

(2) Manager

Example: Physicians may serve as managers of programs, or help in the design of these programs, but when this is not the case physicians with special interest and competence will be needed close to the managerial function.

(3) Skilled Technician

Example: Some physicians will be skilled technicians in this field and all will need some familiarity with the technology of health care of persons not ill.

(4) Teacher-Advisor

Example: Physicians will be involved in teaching patients and the public concerning the uses, capabilities, limitations of programs of prevention and health maintenance, and they will participate more than they do now in patient and public education in such things as nutrition, smoking, weight control and exercises, even though success will continue to be difficult to achieve.

(5) Advocate

Example: Physicians will press for those programs which have an evident and measurable cost benefit to patient and public, and also for research into value received for dollars spent in health care of persons not ill.

be done about whatever problems arise. This competence is rooted in the natural history of disease, injury and emotional disturbance, as this is affected by the characteristics of both the host and his environment, and by current and available methods of prevention and treatment. In Table 1 the primary functions and practice skills of physicians as identified in this report are related to the care of the sick, injured and emotionally disturbed.

(2) Care of persons not ill (Table 2)

The committee believes this will be increasingly a function of allied health personnel and that automated and programmed services for "health maintenance" will play a much larger role in 1980-2000 than is the case today. It is likely that screening, health education, and other health care functions will be carried out by these means, and also that they will be used to help overcome language, cultural and educational barriers to medical and health care. There is widely held opinion that by 1980-2000 patient data health care information will be stored in community or regional computerized data banks, perhaps with the patients themselves as well as authorized physicians and others having access to the data. Physicians will continue to be involved in the care of persons not ill, sometimes directly in the case of those who seek their advice, but more often indirectly in relationship with other health personnel. In Table 2 the primary functions and practice skills of physicians as identified previously are related to the care of persons not ill.

(3) Health care delivery systems (Table 3)

These have become the essential framework or milieu within which the health care of both patients and persons not ill will be carried out. The committee believes that by 1980-2000 it will be fully as important for physicians to understand the health care delivery system or systems, and how they and the various allied health professionals operate within them, as for them to be competent in the art and science of medicine. This suggests that by 1980-2000 most physicians will need more knowledge and competence in the science and technology of health care delivery than they now have. There can be little doubt that the primary functions and practice skills of physicians, as these have been identified,

can and will be applied in relationship to health care delivery systems much as suggested in Table 3.

TABLE 3.—Health Care Delivery Systems

(This includes access to health care, the quantity, quality, and availability of services, cost control, efficiency, effectiveness, cost benefits, etc.)

Professional Opinion

The physician's professional opinion about what is wrong, what is likely to happen and what can be done about it as this pertains to health and its derangements determines much of what use is made of the health care delivery system, and in turn it is to some extent itself determined by the capabilities and limitations of the system. Physicians must understand the health care delivery systems within which they work in order to give a good professional opinion or judgment.

Participant in Decision Making

Physicians as well as consumers and other health personnel will participate in the planning and operation of health care delivery systems. This is necessary if these are to work smoothly and be satisfactory to all concerned. It is expected that this will be the rule rather than the exception in 1980-2000 and will require new competence on the part of physicians.

Procedures and Services *(Practice Skills)*

(1) Problem Solver

Example: Many problems of access, quality, distribution and cost containment can only be solved by or with the help of physicians. This includes centralization and decentralization of services so that alternatives are available, the distribution of physicians and other personnel and the regionalization of certain facilities and services.

(2) Manager

Example: Some physicians may have a managerial role in the planning, operation or evaluation of health care delivery systems but all will help to manage and coordinate continuity of care for their patients within delivery systems.

(3) Skilled Technician

Example: Physicians will perform specialized services in the operation of health care delivery systems. This has already begun with utilization and peer review services being performed by physicians. Technical services of this sort may be expected to multiply as delivery systems become more costly and complex.

(4) Teacher-Advisor

Example: Physicians in the course of their practice will teach and advise their patients, consumers, health personnel and third parties concerning the nature and proper use of health care delivery systems. This will require better knowledge of delivery systems than most physicians now possess.

(5) Advocate

Example: Physicians will advocate the development of better, more effective, higher quality, and more cost efficient delivery systems.

TABLE 4.—Community Health Care

(This includes attention to the social causes of ill health such as poverty, housing, sanitation, education, cultural behavior, transportation barriers, etc.)

Professional Opinion

The professional opinion of the physician, based upon his knowledge of health, its derangements and their causes will be of great importance in community health care. The physician will also need a knowledge and awareness of the subject matter of community and social causes of ill health if his professional opinions and judgments are to have full value.

Participant in Decision Making

Physicians will serve, as they often do now, both as experts and concerned citizens in the decision-making processes of community health care. These functions of physicians will increase in importance for the profession and the community. Physicians who participate in decision making should have the qualifications or credentials needed. Physicians will have greater input on decisions made by the community and government.

Procedures and Services *(Practice Skills)*

(1) Problem Solver

Example: In community health care this will be done with others but the physician can bring his clinical problem solving approach of the history, physical examination, laboratory studies, diagnosis and treatment to bear to identify the "community disease" and to foster community action to correct what is wrong.

(2) Manager

Example: Physicians will be working through organizations more often than alone in community health care and by 1980-2000 community organization for this will be more advanced than it is today. Some physicians will have managerial roles—others will be consulting with management.

(3) Skilled Technician

Example: A few physicians may become skilled technicians in the social causes of ill health but many more will be applying what techniques are available to deal with their consequences. It is expected the medical technology of community health care will have developed much further by 1980-2000 and physicians will be providing many direct services in community health.

(4) Teacher-Advisor

Example: The teacher-advisor role of the physician in community health care is certain to increase. To perform this function effectively physicians will need more knowledge or awareness of the circumstances of poverty, poor housing and sanitation, and of the education, cultural and distance barriers to health and health care in their community than most now have.

(5) Advocate

Example: As physicians become more active in community health care they will become advocates not only of immunizations and planned parenthood, but more strongly of such things as drug abuse programs, education in schools to improve nutrition, to control venereal disease, and to marshal the resources in the community for many new programs to improve community health.

(4) Community health care (Table 4)

Individual physicians have long been concerned with the social causes of ill health. More physicians and the profession as a whole will be more involved by 1980-2000 when rising costs of medical services will focus even greater attention on preventing the need for these services by seeking to reduce or eliminate the social causes of ill health. To perform their essential functions in community health care, physicians should have knowledge of the community in which they are serving, including an understanding of its culture and sensitivities, and know enough of the subject matter of community health care to be able to perform effectively. See Table 4.

(5) Environmental health care (Table 5)

Physicians have been pioneers of progress in environmental health care. By 1980-2000 the involvement of the "composite" physician can only have increased in response to a growing need for more authoritative understanding of health and its derangements in an over-populated and over-polluted closed ecosystem. The committee believes the first task of physicians in this field of health care will be to help to identify the problems of health in the closed ecosystem which exists. These pertain to the numbers of the population and the quality of life they seek to achieve, with its inevitable consumption of the resources of the environment which are finite but reusable and which must be used so that the ecosystem will retain the capability to sustain life and health. Little is yet known about most of these problems. The urgency is considerable, and therefore this is a category of health care in which there is very great need for rapid development. The committee believes that physicians should *now* individually and through their professional organizations take the lead, push for funding for research and for the development of early warning systems. It seems quite likely that research done on closed biological systems in connection with the space program could be useful as a point of departure for some of the research which is needed, as well as other studies now being carried on in crowding and population trends and control of fertility. The approaches will need to be multi-disciplinary. The essential functions of physicians in environmental health care are considered in Table 5.

TABLE 5.—Environmental Health Care

(This includes attention to health in the closed ecosystem; pollution of air, land and water; misuse, overuse or exhaustion of resources essential to health, well-being or life support; and the overall quality of the environment.)

Professional Opinion

The subject matter of environmental health care in this definition should be developing rapidly by 1980-2000, and physicians will be involved because of their knowledge of health and its derangements. Professional opinions by physicians will be needed with respect to what in the environment may be causing ill health and what must be accomplished in the environment to prevent or correct this ill health. Physicians will need to develop competence in the new science of human ecology, whatever this may eventually be called.

Participant in Decision Making

While the physician will be essential to decision making in the field of environmental health care he will participate with others to accomplish this. He will need competence in the subject matter of environmental health in order to participate effectively in decision making in this and each of the other categories of health care considered in this report.

Procedures and Services

(Practice Skills)

(1) Problem Solver

Example: Physicians will be inescapably involved in identifying environmental causes of ill health and what to do about them. They will apply this in practice skills of history, examination, laboratory study, diagnosis and treatment to solving many of these problems.

(2) Manager

Example: Environmental health programs will no doubt require managerial skills of physicians either as managers or in close association with management as is the case in several other categories of health care.

(3) Skilled Technician

Example: Although the subject matter of environmental health care is now largely non-existent, this is likely to develop rapidly, and by 1980-2000 it is probable that environmental health care will require the technical skills of many physicians.

(4) Teacher-Advisor

Example: The composite physician will, among other things, be an environmentalist and will promote a holistic concept of environmental health care as essential for human health. He will advise patients, consumers, communities and the public concerning environmental hazards to health.

(5) Advocate

Example: Initially, physicians will be advocating research in the field of closed biological systems, multidisciplinary approaches to the study of ecosystems, population control, and early warning signals of ecological imbalance which may adversely affect health. Later physicians will advocate application, locally and worldwide, of whatever measures are found to be necessary to assure environmental health.

(6) *Species health care (Table 6)*

Genetic therapy with all of its problems and implications will involve many physicians by 1980-2000. The capability to select the sex of a fetus is already almost on the horizon. Even today the knowledge and technology exists to reduce or remove a number of disease and disability producing genes from the human genetic pool and to eliminate a number of genetic disasters. As previously stated, the mind boggles at what may lie just ahead. When these new technological capabilities are considered in relation to such things as quality of life in a closed ecosystem, limited resources for health care, and the potential technologic capabilities for tampering with the human genetic pool, questions of enormous scientific, social and ethical importance arise. The committee believes that physicians will need a more adequate educational background, not only in the science and the technology which is coming into being, but also in the cultural and ethical considerations which will need to be taken into account. Physicians will be involved in many ways. See Table 6.

C. *Education and Continuing Education for Practice 1980-2000*

In the discussion of "The Practice Situation—1980-2000" and "Medical Practice—1980-2000" just preceding, certain observations were made which suggest that changes may be needed in education and continuing education for practice in 1980-2000. First, and perhaps most important, the body of general knowledge which the "composite" physician should possess will be vastly increased as will the numbers of specialties and specialty situations in which he will practice. Second, what the "composite" physician and even the individual practicing physician needs to know will be far more oriented to the "practice situation" as this is discussed above than is the case today. And third, the rate of change or growth in this body of knowledge, both as it pertains to scientific knowledge and discipline and to the "practice situation," will be extremely rapid, with information of all kinds becoming outdated even more quickly than at present. All of this suggests that fundamental changes may be in order for medical education and continuing education.

It is not the purpose of this report to design

TABLE 6.—*Genetic or Species Health Care*

(This includes attention to the health of the human species as such, including the elimination of bad genes through genetic counselling, and other means of improving the quality of the human race.)

Professional Opinion

Genetic therapy will be a reality by 1980-2000 if not sooner. Physicians will be involved in the use of these techniques more than in their development. Genetic therapy will soon make possible alterations in the human gene pool. The physician's knowledge of health and its derangements inescapably involves him in genetic therapy, species health care and all of their implications. Physicians will need not only a broad awareness but considerable competence in this new field in order to render the professional opinions and judgments which will be needed.

Participant in Decision Making

Physicians, because of their knowledge of health and its derangements will be essential participants in decision making with respect to genetic counselling and species health care. Although decisions will be made by patients, families, communities or the law, physician participation is already essential to the decision-making process, and in the future will be even more so.

Procedures and Services (Practice Skills)

(1) *Problem Solver*

Example: In genetic counselling the physician is a problem solver much as he is in patient care. This role will be expanded as the subject matter of genetic therapy and of species health care is developed. At present a problem to be solved is the further development of this knowledge and technology.

(2) *Manager*

Example: The physician already often acts as manager for the implementation of decisions with respect to genetic counselling. This will be equally or more true of decisions for genetic therapy and of the complex problems of species health care which are now only dimly seen on the horizon but which will be a reality by 1980-2000.

(3) *Skilled Technician*

Example: Physicians will perform many of the technical procedures involved in genetic therapy and species health care just as they do now. As new skills are developed and come into use physicians must add these to their awareness and competence.

(4) *Teacher-Advisor*

Example: Physicians already act as teachers and advisors to patients and their families in genetic counselling. As knowledge of the subject matter grows this role will increase and be extended to communities and public.

(5) *Advocate*

Example: Many physicians have already assumed a role of advocacy with respect to population control in terms of quantity, and as their knowledge and competence in genetic and species health care increases, physicians will surely advocate improvement in the quality of the population beginning with the elimination of bad genes and later, no doubt, in other ways to be made possible by the use of technology not yet developed.

whatever changes may be needed in medical education nor is the committee competent to do this, but a few comments and suggestions may be in order which might be considered further by both the practicing profession and medical educators.

1. If it is true that the essential functions of the physician in 1980-2000 will be as described (a) rendering of professional opinions, (b) participating in the decision-making processes throughout the spectrum of health care, and (c) performing services and procedures by exercising practice skills as problem solvers, managers, technicians, teachers and advocates in various ways throughout the spectrum of health care—then *all* physicians should have a degree of professional awareness of the entire body of general knowledge of health and health care, to a degree more or less comparable to the awareness they now have of the various specialties of medicine, and in addition they should have a special competence in one or more specialized segments of the whole. If this is to be done some modification will be needed of the present trend in medical education which seems to be toward very early specialization and away from the idea that there is a core of general knowledge, experience or expertise which all physicians should possess, regardless of specialty.

2. The degree of “practice situation” orientation which seems likely in the physician’s practice by 1980-2000 suggests that medical education itself should become much more “practice-situation” oriented. This would suggest that medical students and young physicians particularly should be taught more about what is involved in the scope of medicine, the nature of the conceptual, logistical, ethical and regulatory forces impinging upon health and health care which are described earlier in this report, and how better to deal with them as they shift and change during their life of practice. This would involve the introduction of academic and practical educational experiences not now regarded as appropriately a part of medical education. The orientation of education toward the “practice situation” will no doubt cause the production of specialists of various kinds to more nearly reflect the needs of health care than of the educational institutions as is apt to be the case today.

3. If one combines the need to link medical education more closely to this “practice situation,” as this has been described, with the

rapidly increasing rate of growth and change in both the scientific and “practice situation” aspects of professional knowledge and expertise, this suggests that all physicians at all levels of experience will be striving to keep up with the same new progress at much the same time. One wonders if indeed medical education and continuing education will not actually begin to coalesce, and if the time is not soon to come when both students and practicing physicians will be needing to learn many of the same new things at virtually the same time. It could result in a more common educational endeavor for medical students and practicing physicians, either in medical school or community settings or both, and one could conceive of a rather different approach to the concept of both the student body and a medical curriculum. Perhaps exploration of some of these possibilities might be begun on an experimental basis.

D. Incentives for Physicians 1980-2000

It seems clear from what has been presented in this report that the needs of society, medical practice and medical education will undergo change and that this is absolutely necessary for the viability of any acceptable system or systems of medical care. The problems of distribution of physicians and health care services have to be solved. There has to be new extensive experimentation with different organizational forms of medical practice. Automation, multiphasic health testing, and computer-assisted services may have to be used in health care even though their cost effectiveness may sometimes be open to question. Consumers may *have* to be brought even more directly, along with physicians and others, into the decision making and managerial functions in most aspects of health care despite their relative lack of technical expertise. There will certainly be new dimensions of social as well as physician involvement throughout the whole spectrum of health care, including medical education as well as the practice situation.

The committee devoted a part of its discussions to what might be the incentives for physicians to practice in the situation as this has been projected for 1980-2000. In summarizing these discussions the committee considers (1) compulsion, which at the very least would have an adverse effect on many who would otherwise choose medicine as a career, (2) negative incen-

tives, which already may be having an adverse effect upon efficiency, if not productivity, in the delivery of health care services, (3) positive incentives, which will need to be maintained and perhaps strengthened if delivery of health care services by physicians and others is to be efficient and satisfactory, and (4) personal goals, which many if not most physicians seek to satisfy when they choose medicine for their professional career.

(1) *Compulsion*

The thought or rather the specter of compulsion kept reappearing throughout the committee's deliberations. It occurred most often in connection with the distribution of physicians to rural and urban ghetto areas now inadequately served, and whether or not compulsory service will be required of physicians in such areas, either as part of their education or as some kind of required national service. But the committee was also informed that in one of the provinces of Canada it recently became illegal for a physician either to leave the province or not to continue in his active practice. Compulsion, then, has been used in neighboring Canada to retain physicians in practice. While the idea of compulsory service by physicians in the United States is not easily disregarded, the committee believes there is real hope for other and better solutions. Egalitarianism as it exists today in the United States is not likely to find compulsion acceptable for either physicians or patients. Furthermore, physicians, like other human beings, do not work well under compulsion, and physicians' services rendered under these conditions are not likely to be satisfactory to themselves, to patients or to the public. The committee is convinced that this nation will have found more sophisticated solutions than compulsion to overcome the problems of distribution of medical and other health care services by 1980-2000.

(2) *Negative incentives*

Negative incentives for physicians, or deterrents which tend to reduce their interest or effectiveness in practice situations, are increasing. Their effect on physician productivity and the quality and the cost of medical care remains unmeasured. However, if present trends continue, there will surely be serious obstacles and barriers to the efficient and economic delivery of

health care of high quality by 1980-2000. The growth in time-consuming, wasteful administrative paper work, required to satisfy government and third parties, has already eroded the quality and added to the cost of health care in many ways. The threat or actuality of malpractice suits, often of dubious purpose and validity, is negative incentive of increasing significance. The prospect of action at law often causes the physician to give high priority to his own legal defense as he provides care for his patients. Because of this some patients may be denied the possibility of benefiting from a somewhat risky procedure, or conversely may be required to undergo procedures which would be unnecessary were it not for the possibility of later litigation. Harassment of the profession, which now seems to have become sort of the thing to do for both government and the public press, can become a significant negative incentive if carried too far. Physicians in practice, as well as those who might be considering medicine as their life work, are affected adversely and this reflects in patient care. While some may say these are clouds only on the horizon, it seems to many physicians that they are overhead and that they have already begun to ominously darken the skies of medicine and health care. The committee hopes that the weather in which physicians will practice 1980-2000 will show signs of some clearing as far as these kinds of negative incentives are concerned, but from present indications this seems not too likely.

(3) *Positive incentives*

A stimulating intellectual, professional and social environment, a balanced life-style appropriate to their hard-earned professional status, and a satisfactory pecuniary reward are important and indeed essential positive incentives for most physicians, and, if not for them, they usually are for their families. Physicians derive enormous satisfaction from a sense of skillful accomplishment in patient care, and this should not be underrated. But they are also influenced, though in a different way, by the method by which they are paid. Like others who render services of various kinds, the physician will necessarily need to satisfy whomever pays for his services. If he is paid by the patient, he must satisfy the patient; if by the government, he must satisfy the government; if by capitation, he may strive to

conserve his energies in the face of more or less insatiable demands. Also, physicians are very much like other people, and if they are paid by salary, there is little incentive to increase productivity, and if by fee-for-service, then productivity tends to increase. It is clear that how the physician is paid, how much he is paid and the circumstances of his practice and his living situation are important incentives for physicians in the care of patients. And if the reasoning in this report is valid, it will soon be necessary to develop reasonable and satisfactory incentives, pecuniary and otherwise, for the various other essential functions the physician will start to perform elsewhere throughout the spectrum of health care. Medical care will surely be better and quite likely less costly overall if the positive incentives for physicians are kept strong.

(4) *Personal goals*

The data from medical schools indicate that the great majority of men and women who enter medicine say they do so because they are interested in science, often particularly biological science, and also wish to do something tangible to help their fellow man on an individual and personal basis. These personal goals are shared by many, if not most physicians, and their satisfaction becomes a principal aim for their life work. Such personal goals are what draw intelligent and energetic young people to a profession which requires longer training and harder work for the same kind of pecuniary and worldly reward which, with their talents and energy, such persons might reasonably be expected to acquire much more quickly and easily in some less demanding way. Other, and probably less deeply rooted, goals are the satisfactions of being respected in the community, of helping others solve problems they cannot solve themselves, and of personal accomplishment. But this is not always the case, and possibly may be less so in the future. There is some evidence that some younger physicians may be more concerned with their personal growth and fulfillment when they seek a medical education, and their personal goals may not include much in the way of the usual incentive to practice. Such students and young physicians appear to be a minority, however. It is likely that in 1980-2000 the traditional personal goals, including the very deep desire to be of service to their fellow man, will still be

powerful incentives for most physicians, and the fascination of new and fantastic developments in medical and health science will continue to draw intelligent and energetic young persons to a profession which will be reaching out to perform the many vital functions of the "composite" physician 1980-2000.

VII. Summary and Recommendations

This report of the Committee on the Role of Medicine in Society has addressed itself to what the committee foresees will be the situation of the "Physician and His Practice in 1980-2000." It has identified conceptual, logistical, ethical and regulatory forces which it believes will decisively influence the practice situation at that time. The problems to be solved in the 1970's have been outlined as the committee sees them. Some predictions for 1980-2000 have been offered. An assessment of the situation in which the physician may find himself is given: the scope of medicine as it is envisioned for 1980-2000 is delineated and the essential functions of physicians are described and then applied to the scope of medicine as envisioned. Education and continuing education for practice 1980-2000 are discussed and likely incentives for practice by the end of this century are briefly considered.

Recommendations

A. *The essential functions of the physician*

(1) The committee recommends that the essential functions of the physician in the spectrum of health care as these have been developed in this report be recognized and studied by the medical profession, by medical educators and by government. These essential functions are:

- (a) to render professional opinions concerning health and its derangements,
- (b) to participate in decision making at all levels of health care,
- (c) to perform procedures and services in health care using practice skills as problem solver, manager, skilled technician, teacher or advisor, and advocate.

B. *Health care delivery*

(2) The committee recommends that ways be sought to define more precisely many of

the terms used in components of health care delivery as an essential first step toward a more rational and effective approach to this complex problem.

(3) The committee recommends that methods be developed for continuing assessment of logistical trends affecting the supply of and demand for health care services.

(4) The committee recommends that prompt attention be given to developing a better health manpower structure which will relate the functions of various health professionals more closely to one another, provide greater upward and lateral mobility, and lessen the likelihood of fractionation and multiple standards of care.

(5) The committee recommends that steps be taken to develop better methods of assessing the effectiveness and cost benefit of services and resources throughout the spectrum of health care as an essential prerequisite to the evolution of a more rational and economic delivery system.

(6) The committee recommends that ways be sought to identify and quantify the socially engendered causes of ill health and to publicize their effect on health and the resultant costs of health care services.

(7) The committee recommends that physicians and medical organizations be encouraged to participate actively in the planning, operation and evaluation of health care programs, plans and systems of all kinds.

(8) The committee recommends that physicians and medical organizations concern themselves more actively with the evolution of ethical value systems as these will develop for health care.

(9) The committee recommends that physicians find ways to overcome barriers to the development of the physician-patient relationship in the face of automation, health teams, programmed services and trends toward depersonalization and dehumanization of health care.

(10) The committee recommends that further research into health care delivery be encouraged and that this be carried on

throughout the spectrum of health care with special emphasis at this time on the care of persons not ill and the problems of health in the closed ecosystem.

(11) The committee recommends that the medical profession assume initiative and in collaboration with others promote the development of a national health policy which will begin to delineate roles and responsibilities of health personnel, and recommend allocation of resources, and thus bring into being a multidisciplinary coordinated systems approach to the problems of acquiring, assimilating and applying knowledge for better health and better health care.

(12) The committee recommends that attention be given to identifying and providing appropriate compensation for many of the professional services physicians will render throughout the spectrum of health care which are not being compensated at present.

C. *Medical education*

(13) The committee recommends that the essential functions of the physician as described in this report be included in educational programs preparing physicians for the practice situation 1980-2000.

(14) The committee recommends that a physician's education provide him a broad knowledge of health and its derangements and a broad awareness of the capabilities and limitations of health care services throughout the spectrum of health care.

(15) The committee recommends that medical education include some consideration of the conceptual, logistical, ethical and regulatory forces affecting health care, the characteristics of human behavior and human society, and the nature of the ecological relationships between man and his environment.

(16) The committee recommends that training directed toward a specialty in practice be based upon a broad rather than a specialized background of medical education in order that all physicians may be adequately prepared to carry out their essential functions.

(17) The committee recommends that consideration be given to experiments in which the education of medical students, interns and residents, and practicing physicians might be combined for selected topics where change is occurring rapidly and all need to acquire much the same new information at much the same time.

D. *Organized medicine*

(18) The committee recommends that the American Medical Association and its constituent and component medical societies be viewed as the embodiment of the "composite" physician and therefore recommends that medical organizations as a body perform the appropriate essential functions of the "composite" physician *vis-a-vis* society throughout the spectrum of health care.

(19) The committee recommends that the AMA and its constituent and component medical societies and other medical organizations develop a greater responsiveness to the needs and opinions of the public and their own members, and that consumers, other providers and their own members be given a larger role in decision-making processes.

(20) The committee recommends that the medical profession continue to seek incentives which will draw young persons with intelligence and energy to practice a profes-

sion which will be reaching out to perform the many essential functions of the "composite" physician in 1980-2000.

Committee on the Role of Medicine in Society

RALPH W. BURNETT, M.D.
JOHN B. DILLON, M.D.
SANFORD FELDMAN, M.D.
FOREST J. GRUNIGEN, M.D.
M. M. HASKELL, M.D.
R. HEWLETT LEE, M.D.
MARVIN J. SHAPIRO, M.D.
MALCOLM C. TODD, M.D.
MALCOLM S. M. WATTS, M.D., *Chairman*

Ex-Officio Members

HENRY V. EASTMAN, M.D.
E. KASH ROSE, M.D.

Consultants

BURT L. DAVIS, M.D.
JOHN T. SAIDY, M.D.

Medical Student Members

PAUL BARRETT, *University of Southern California*
LARRY FREEMAN, *University of California, Irvine*
WILLIAM GILLANDERS, *University of California, San Francisco*
WILLIAM NOWACK, *Stanford University*
GEOFFREY SMITH, *University of California, Davis*
STEPHEN TEXTOR, *University of California, Los Angeles*
BRUCE WINTERS, *Loma Linda University*

Alternate representatives to the committee who also contributed were:

SUSAN BAILEY, *University of Southern California*
WILLIAM REINER, *University of California, Irvine*
MITSUO TOMITA, *University of California, San Francisco*
HANS DANKERS, *Stanford University*
JON MANDELBAUM, *University of California, Davis*
NICK PUTNAM, *University of California, Los Angeles*
GEORGE SIMPSON, *Loma Linda University*

Informed Opinion

Reflections on Medi-Cal

CAREL E. H. MULDER, *Sacramento*

FROM TIME IMMEMORIAL our country has been blessed with a plenitude of politicians, professional and amateur, whose principal stock in trade is the simplistic solution of extremely complex problems. Peddling and buying this stock calls for the ability to close one's eyes to some obvious facts of life, or if forced to recognize them, to take the position that such "minor problems" will be solved by administrative action of the bureaucracy, or will somehow solve themselves.

There are few who deny that Society has the obligation to enable all its members to have the benefit of optimum health. Our technology has made immense strides to bring us closer to this goal. But the application of this technology to the execution of our societal tasks has been a succession of trials and errors. We have often worked at cross purposes; and have frequently ignored some basic laws of economics and of human behavior.

Until 1950 health care for the poor was generally a matter of public and private charity. In that year the Social Security Act was amended to permit "vendor payments" for health care. This enactment in effect pronounced the ultimate death sentence on private charity: it heralded the day when every item of health service became something to be bartered. The 1956 amendments poured large amounts of federal and state money into this concept; the 1960 Kerr-Mills enactment expanded on it.

The author is Consultant in Health Care Administration, Sacramento.

Reprint requests to: C. E. H. Mulder, 8901 Woodman Way, Sacramento, Ca. 95826.

But 1965 was the year when the politicians in Congress really delivered on their Utopian promises: the Congressional enactment of Medicare and Medicaid. In the course of deliberations the going was so good that the long-pending proposal for hospital insurance was quickly dilated to include supplementary medical insurance and MAA (Kerr-Mills) was expanded into a potentially comprehensive coverage for nearly all poor or near-poor individuals and families.

In their efforts to be all things to all men the lawmakers, with careless abandon, added an assortment of goodies to the recipe: free choice of provider, encouragement to states to include chiropractic and similar questionable services, full cost institutional reimbursement, usual and customary charges, requirements to launch fairly full-blown programs, prohibitions against liens and against the assessment of liability on the children of aged (regardless of their financial situation), an unrealistic goal of global coverage of all poor by 1975, the use of existing fiscal intermediaries and carriers, and many others.

Viewed severally these provisions are not without merit; in principle, and if applied gradually and with a modicum of realism, they could have strengthened our ability to furnish adequate preventive, diagnostic, therapeutic and rehabilitative services to the poor. But somehow our elected and appointed officials, as well as many in the health industry, were carried away by a psychogenic optimism that the aggregate of all bright ideas must be brought to bear, untried and undiluted, on the Medicare-Medicaid brainchild. It

remained for time and the emergence of some ignored facts to test the programs so hastily conceived and born.

Ignored facts inherently are seen more clearly through hindsight than through foresight. There were voices in the wilderness, not all self-serving, that pleaded for less haste and more thought. By now, some six or seven years later, hindsight tells us that these voices were not unduly pessimistic and that they deserved more recognition than they received; that we really may well have indulged in too much too soon.

What appear to be some of these ignored facts?

1. The infusion of massive public financing into a system of low supply and high demand is by nature inflationary.

2. The historic phenomenon that many poor will forego the cash benefits of the welfare system is not equally true for health care benefits.

3. A system which has developed without much internal control cannot be expected to enthusiastically embrace the imposition of controls from without, or to suddenly generate effective controls from within.

4. A small percentage of any group will not hesitate to make a dishonest buck, but a much larger percentage will make an honest buck (that is, without willful violation of conscience or statute) if it is within easy reach.

5. When experts disagree on what constitutes an adequate health care system, millions of under-educated persons cannot be expected to make an intelligent use of the system(s) suddenly made available to them.

6. Professionalism is frequently tainted by a measure of jealousy and greed.

7. An economic slump is bound to aggravate these problems in near-geometric progression.

In September of 1967 a meeting of Medicaid administrators from the larger states was convened in San Francisco to consider ways and means of dealing with these facts without destroying the basic structure created by the people's elected representatives. Unfortunately this meeting quickly acquired a distinctly political flavor and, since many Medicaid administrators are, *de facto*, political creatures also, with the ability to ignore facts or problems or to zero in on one of them to the exclusion of others, the overwhelming majority of conferees saw no problems ahead.

Although there were times that tried men's souls, I am not ashamed of Medi-Cal's history.* We worked cooperatively with providers and beneficiaries, maintaining an objective view; we did our best to get the taxpayer the most for his dollar; we went after the few crooks; we encouraged the fiscal intermediaries to pay faster, more accurately, and to review utilization through professionally advised screening mechanisms, computerized for optimum yield. Although the outcome of all this, in terms of improved health of the poor, and in terms of cost-effectiveness, is hard to measure, I do know that more people obtained easier access to a higher quality of care than ever before in California history.

We made some friends, we made some enemies; but above all we did our duty to administer a difficult and imperfect statute with the utmost honesty. We managed to stabilize costs. The cost of care per person on the rolls leveled off in 1969 and remained level.

Why then have things gone from bad to worse? Why the finger of scorn pointing at recipients, providers, administrators, intermediaries? Here again the answer must be sought largely in the areas of economics and politics. One effect of the worsened national economy has been a spectacular increase in the number of persons who qualify for welfare and Medicaid. Concurrently tax revenues began to decline. The concept of welfare benefits as a right rather than a privilege led to stricter judicial interpretations of the "equal protection" and similar clauses in our Constitution. Closed end appropriations, optimistically computed on underestimated assumptions, proved insufficient to care for the influx of applicants. Rolling outstanding obligations forward to the next fiscal year provided no real relief, a lesson most of us have learned at some time in our private lives.

As a result the priorities around which all governmental taxing and spending programs are built became the object of scrutiny. Observers in the political field had noted, during the past decade, a decline in the voters' support for programs serving the poor and underprivileged. Some politicians construed this as a mandate to assign these programs the lowest possible priority. This posture is reflected in the Welfare

*Note: The author was Director of California State Department of Health Care Services, 1967-1970.

and Medi-Cal proposals as introduced by the State Administration. It is also reflected in the Administration's stance on Tax Reform: i.e. do not deprive the rich and the vested interests of existing tax benefits and loopholes.

Notwithstanding negotiated modifications in these proposals and findings of unconstitutionality and non-conformity with Federal law by the courts, the fact remains that welfare and medical assistance benefits are substantially impaired under the amended statute. In addition, Medi-Cal may well be underfunded in the current Budget unless there is a further decline in case loads.

If federal law had been less rigid the problem could have been painfully but forthrightly resolved by reducing the benefit structure. Instead, the problem was resolved by leaving the semblance of a comprehensive mainstream program on the statute books, but heavily encumbered by a plethora of unprecedented restrictions and procedural obstacles. Many of these tend, in fact, to interfere with the appropriate exercise of professional judgment, to reduce the status of the community physician to that of the neophyte intern. These restrictions discourage both providers and recipients, and increase the cost of administration, eroding the savings derived from constantly improving electronic data processing techniques achieved by the fiscal intermediary and his subcontractor.

There is no doubt that the reformed program will result in a decrease in program expenditures. Whether the decrease will be sufficient to remain within the General Fund appropriation will become known toward the end of the fiscal year. The real cost of this unfortunate re-direction of the program will be inestimable: later costs generated by delay in needed care, costs in quality occasioned by a shift in participation from fully qualified practitioners to the marginal operators who will take Medi-Cal patients no matter how the game is played; the intangible cost of giving a bewildered poverty population the impression that society really does not care what happens to them.

No one is satisfied with the situation as it stands—not even those who wrought it. Government, industry and consumers are back at the drawing boards to find the solution; working, as usual, at cross purposes. The search for the simplistic solution focuses on such things as increas-

ing the supply of physicians, compulsory health insurance, tax credits, abolition of fee-for-service, Health Maintenance Organizations, a National Health Plan. All are touted as the wonder drugs of choice. There may well be some merit to each of these, but . . .

I wish I could close with a specific prescription; and if I were a politician I would feel it my duty to do so, regardless of ability. All I can do at this point is to again point the finger to the past and to express the hope that we'll find solutions by searching in an orderly and thoughtful way. It would be unwise to scrap the entire existing system and to embark on a new experiment *de novo*: evolution can produce more worthwhile results than revolution.

There is no doubt that inappropriate utilization has been and continues to be the principal problem of mainstream care. Setting up prepaid health plans, health maintenance organizations, requirements for prior authorization and co-payments will not resolve *this* problem. It can be resolved only by intensifying the current work of medical societies and foundations in the area of peer review. Leading practitioners, in collaboration with their academic and administrative colleagues, should develop a massive compendium of model treatment plans against which billings can be audited before payment. Our technology has reached the point where this audit can be automated, thus quickly and inexpensively segregating the billings which require professional attention or referral to peer groups. This system should be used not only for Medicare and Medi-Cal, but for all third party payment programs. The legislature wisely provided that such a system should be initiated in selected locations to parallel the more expensive one now used by the state of California. I hope the Department of Health Care Services will soon request Blue Shield and the Blue Crosses to implement this provision.

In addition it must be recognized that a reasonable degree of government monitoring of the delivery system is desirable to assure that the distribution of professional and institutional resources is properly aligned with demonstrated needs, to eradicate inordinate profits on goods and services, and to promote optimum efficiency and cost-effectiveness.

The American people, rich and poor alike, are entitled to this.

Medical Education

The Foreign Medical Graduate in California

JOHN R. BELJAN, M.D., *Davis*

THE "PROBLEM" OF THE foreign medical graduate is very complex and has local, national, and international political implications. Considerable factual data concerning the foreign medical graduate has been developed in a number of resource documents which have been freely utilized in the development of this report. In addition to those listed in the reference section of this article, resource documents include the California State Business and Professions Code, personal communications, and a wide variety of journal articles and other references which have come to our attention.

Unquestionably, a real need exists for the foreign medical graduate pool to alleviate the national health manpower shortage in the United States, and this need is expected to increase rather than to plateau. In fact, intake of foreign medical school graduates has been increasing annually. Thus, licensure, training, and practice for the foreign medical graduate will be with us for the foreseeable future.

Finally, a very important distinction must be made between the foreign medical graduate who is a citizen of the United States and one who is not. There are considerable differences in California relative to citizenship status and medical licensure, and this local practice is generally reflected in the licensure philosophy of the majority of the nation's state licensing boards.

Need

Graduates of foreign medical schools substantially augment the number of physicians licensed

annually in the United States. In some states, the majority of new licentiates are foreign medical graduates due to the continuing westward migration of domestically-trained licensed physicians. (Seventy percent of this state's practicing physicians are trained outside California.) As of early 1971, foreign medical graduates represented 35.6 percent of New York's physicians, in contrast to California's 7.2 percent. A continuing influx of foreign medical graduates is planned upon by governmental projections for national health manpower, and all available evidence indicates that the numbers involved in this annual influx will continue to increase.

At present more than 3,000 foreign medical graduates immigrate to the United States yearly, and in 1970 32 percent of the new licenses granted in the United States went to foreign medical graduates. (As a corollary, foreign medical graduates made up 32 percent of the total of interns and residents for this same period.) In 1960, 14,768 applicants took the Educational Council for Foreign Medical Graduates (ECFMG) examination and 1,419 foreign medical graduates were newly licensed. In 1970, the figures rose to 29,950 and 3,036, respectively. Thus, in the period of only one decade, there has been a doubling of both the numbers taking the ECFMG examination and those newly licensed by the various licensure boards in the United States.

Although many surveys would indicate that the number of newly-licensed foreign medical graduates would seem fairly constant at about the 3,000 mark, experience indicates that there has been an annual increase in actual number over the past decade, and certain 1968 changes

Reprint requests to: J. R. Beljan, M.D., Assistant Dean, University of California, Davis, School of Medicine, Davis, Ca. 95616.

relative to the Immigration Act and student visas will encourage increasing numbers of foreign medical graduates to enter the United States on a permanent basis. The American Medical Association document indicates that a figure of 4,000 as the annual addition of foreign-trained physicians to the domestic health manpower pool as an estimation might better be increased to 5,000 or 6,000 a year for more valid projections.

In addition a large number of United States citizens are studying medicine abroad. Most estimates indicate this group is more than 3,000, with over 500 new students commencing medical education abroad each year, and over 200 obtaining medical degrees and U.S. licensure. There have been recent steps taken to enhance the ability of U.S. nationals studying abroad to re-enter AMA-approved internships and residency programs. These will be outlined subsequently, but the system is somewhat cumbersome and entails delays for the applicant. California law provides an easier route to licensure for foreign medical graduates if they are U.S. citizens or have filed a petition for naturalization. In any event, additional health manpower does exist in the form of U.S. nationals studying medicine abroad, and there is a need to ensure that licensure can be obtained reasonably and expeditiously in California by qualified candidates.

Licensure Experience

There is an increasing number of new applicants and licentiates from the foreign medical graduate pool (both U.S. nationals and aliens) and those seeking U.S. licensure must successfully complete at least two (and sometimes three) examinations: (1) ECFMG (either in fact, or, as in California, *de facto*), (2) a State Board licensure examination, (3) a State Board re-examination in another state, because of reciprocity barriers.

An annually increasing pool of foreign medical graduates is clearly indicated by the 1970 licensure examination statistics compiled by the AMA. Of 12,198 applicants for licensure by written examination given by 53 medical examining boards in 1970, 5,543 were graduates of approved schools of the United States and Canada, while 6,236 were foreign medical graduates, an increase of 1,322 foreign graduates over the previous year. The year 1970 was the first in which there was an absolute majority of foreign over

domestic medical graduate applicants for state licensure examinations. (Nationally, however, the failure rate in this group was four times that of U.S. and Canadian medical school graduates—a proportion that has been annually consistent. For the 349 foreign medical schools represented in 1970, the failure rate overall was 2,331 (37.3 percent) of the 6,236 examinees.)

In California, 205 foreign medical graduates were examined; 90 passed and 115 (56 percent) failed. Graduates of U.S. and Canadian schools taking the California licensure examination numbered 221; 206 passed and 15 (7 percent) failed. Thus in 1970 the California failure rate for foreign graduates was six times as high as for graduates here and in Canada, and of the 3,308 licenses issued, only 311 were by California State Board examination, while 2,997 were issued by reciprocity and endorsement (including National Board credentials).

With respect to the ECFMG examination, the scores of individual candidates who have taken several examinations tend to remain quite constant, but overall pass-rates will vary considerably. In 1970, a total of 29,950 examinations were administered, with 11,916 (39.8 percent) passing; in 1971, only 9,693 (31.2 percent) of the 31,033 examinees passed. Of the 29,950 taking the examination in 1970, only 5,436 were certified by the ECFMG. About three-fourths of these Standard Certificates were issued to candidates who were already in the United States, presumably in an internship or residency on the basis of an Interim ECFMG Certificate. The fact that 3,036 ECFMG-certificated individuals were newly licensed in 1970 represents, in part, the time lag between an individual's ECFMG certification and his ultimate licensure in the United States.

It should be pointed out that the passing rate for the ECFMG is not much better for U.S. citizens studying abroad than it is for foreign nationals. The AMA figures for 1970 show only three schools had as many as 25 American citizens taking the ECFMG of September 16, 1970. There were 26 candidates from the Catholic University of Louvain, of whom 14 passed; 143 from the University of Bologna, of whom 26 passed; and 41 from the University of Rome, of whom 28 passed. These figures suggest that some caution must be exercised in considering the case of U.S. nationals graduating from foreign medical schools who seek licensure in the United States.

Foreign Medical Graduates (U.S. Nationals)

There is no doubt that the American citizen studying medicine at a foreign medical school represents a specific problem. As the number of qualified applicants unable to find places in American medical schools increases, it is likely that more candidates will turn to medical studies in foreign schools. The largest numbers at present are at the Autonomous University of Guadalajara in Mexico and the University of Bologna in Italy. Most of these expatriates will seek to return to practice in the United States. However, as already indicated, the performance of these students on the ECFMG examinations has been disappointing.

A new policy recently adopted by the ECFMG Board of Trustees makes it no longer necessary for a foreign medical graduate to take both the ECFMG examination and the California State Board Examination (FLEX*) as a prerequisite for an internship in California. This new policy provides that ECFMG certification may be awarded to foreign medical graduates who have completed the ECFMG educational requirements and who have received passing grades (75 or better) on FLEX. This policy will not apply to students from Mexico who do not complete educational requirements leading to the *Titulo de Medico Cirujano*.

Recent legislation in California could enable American citizens studying abroad to bypass ECFMG certification in the specific case of the Guadalajara graduate. Though commendable in its intent, legislation of this type could threaten the Educational Council for Foreign Medical Graduates, which was a service born of necessity.

Nonetheless, the Report on Physician Manpower and Medical Education from the American Medical Association makes the following statement:

It is recommended that the AMA reaffirm its support of the Educational Council for Foreign Medical Graduates in its task of ensuring minimal standards for physicians trained in foreign schools and seeking graduate medical education in the United States, and intense efforts be continued to assist the repatriation of American students studying in foreign medical schools.

*Federation Licensing Examination, a standardized examination used by the medical licensure boards of a number of states.

The question of reciprocity licensure in California for foreign medical graduates (both U.S. nationals and aliens) can be dispensed with briefly. Essentially, there is none. With the advent of the ECFMG, the AMA Council on Medical Education and the Executive Council of the Association of American Medical Colleges no longer publish a listing of "approved" foreign medical schools. Section 2310 of the California Medical Practice Act in Article 11 (Reciprocity) requires a "degree of doctor of medicine after the completion of a full course of study as prescribed by this chapter in an approved medical school." This section had been interpreted by the State Board of Medical Examiners in its broadest sense—that is, foreign medical schools are not "approved schools" in the eyes of the Board.

There are, however, several pathways by which a foreign medical graduate may enter AMA-approved internship and residency programs. Basic concepts of medical licensure are usually related to an examination and a required period of approved graduate experience; thus, accreditation of approved internship and residency programs is closely intertwined with licensure eligibility. At present, five ways by which a foreign-trained individual can now enter such programs exist:

1. **COTRANS.** The COTRANS Program consists of admission with advanced standing to an approved U.S. or Canadian medical school. In this instance, on an individual basis, the State Board of Medical Examiners of California has admitted candidates to licensure examination when transfer has occurred from an extra-national to a domestic medical school, and the applicant has completed at least two years in the approved medical school in the United States.
2. **ECFMG Certification.** This is the "normal" and usual pathway for the foreign medical graduate to U.S. medicine. Certification by the ECFMG is granted on the basis of satisfying the ECFMG educational requirements as well as passing the ECFMG examination. Admission to the ECFMG examination is available to any bona fide student in any medical school listed in the W.H.O. Directory of Medical Schools (except the native practitioner school in Fiji). Once a candidate has passed the examination, he may receive ECFMG certification following

completion of all of the educational requirements for a license to practice medicine in the country of his training. This policy stipulation has led to certain complications for U.S. nationals attending schools having internship and social service requirements as integral parts of their medical curricula.

3. *U.S. Licensure.* The provision exists that a person who has obtained a full and unrestricted license to practice medicine, issued by a state or other U.S. jurisdiction authorized to license physicians, may enter graduate programs directly. Such a person, however, would not be normally qualified for a reciprocity certificate in California without additional service and examination (depending on particular individual circumstances).
4. *Licensure (U.S. Citizens).* For American citizens, graduate programs may be entered following the successful completion of a licensure examination in a state where a full and unrestricted license will be issued to the candidate after satisfactory completion of an internship or residency in that state without further examination. To be eligible for this route, the foreign medical graduate must have completed all educational requirements that would make him eligible for ECFMG certification should he choose to apply. (This pathway is not compatible with Section 2193.7 of the California Medical Practice Act, created in 1970 by Assembly Bill 37 [Lanterman]. This will be discussed in later paragraphs under the heading, State Legislation and Implications.)
5. *Supervised Clinical Training.* This is a new pathway which was approved July 1, 1971. It is obviously intended to provide increased clinical exposure and enhanced medical training before entrance into approved internship programs. Briefly, it is as follows:

If a United States citizen has (a) completed successfully his undergraduate pre-medical work in an accredited American college or university and (b) has studied in a medical school outside the United States recognized by the World Health Organization, and (c) has completed all formal requirements of the foreign medical school except internship and/or social service, and (d) has passed a suitable screening examination, he

may then (e) substitute an academic year of supervised clinical training before his first year of an AMA-approved graduate program without a social service obligation or a requirement for an ECFMG certificate.

It should be pointed out that ECFMG certification is not specifically required by California law for medical licensure. (This is also the case with six other state licensure boards.) However, the possible loss of hospital accreditation and house officer training programs has, in point of fact, resulted in a *de facto* requirement for ECFMG certification for certain individuals.

Additionally, although U.S. citizenship is not a specific requirement for medical licensure in California, citizenship does significantly ease licensure requirements. For example, a foreign medical graduate who is (1) a citizen of the United States or (2) an alien who has filed a declaration of citizenship and has been engaged in the practice of medicine in the United States for at least five years in hospitals approved by the Board for the training of interns, need only pass the complete State examination and serve a year's hospital service acceptable to the Board. He must, however, successfully negotiate the written examination "prior to commencing an internship in a hospital located in this State or at any time after the satisfactory completion of an internship in an approved hospital located in another state, and must also pass an oral and clinical examination at the satisfactory completion of the one-year internship."

This specific point has led to certain problems for Guadalajara graduates, since the ECFMG policy is that a graduate of any foreign medical school, regardless of his nationality, is not eligible for ECFMG certification and appointment to an approved United States internship until he has completed the prescribed educational requirements. In the case of Guadalajara graduates, this has been interpreted by the ECFMG as eligibility for the *Titulo de Medico Cirujano*, which requires a year's internship followed by a year of social service.

Foreign Medical Graduates (Non-U.S. Nationals)

Many of the comments made in the previous section have application to this category of foreign medical graduate. If a person has had

training and experience in the United States and has filed a declaration of citizenship or a petition for naturalization, he would qualify as noted above. However, if a foreign medical graduate applicant is not an American citizen, he must have been admitted to the practice of medicine "in the country wherein is located the institution at which he has completed the resident courses of professional instruction required. . . ." Additionally, he must serve at least two years in a service satisfactory to the Board, one year of which must have been accomplished in a hospital in California. Furthermore, he must pass the written examination before starting an internship in this state, and "must also pass the oral and clinical examination at the satisfactory completion of the two-year internship period." The normal route for licensure in California for foreign medical school graduates (non-U.S. national) is through the ECFMG certification process, followed by completion of the above requirements.

It is important to insert an historical note at this point for future reference. Until 1960, the AMA Council on Medical Education and the Executive Council of the Association of American Medical Colleges published a listing of foreign medical schools whose graduates were recommended for licensure consideration on the same basis as domestic graduates (1950-1960). This was utilized as an advisory list by licensure boards and hospitals, but there were many problems with regard to adequate evaluation of individual graduates. With the ultimate development of the ECFMG, this listing was withdrawn on January 1, 1960, and the chaos that existed in the decade before was greatly ameliorated by the successful operation of the ECFMG certification process. This point is important to keep in mind because if the ECFMG were to be compromised, considerable difficulty in assessing the adequacy of a foreign medical graduate's education would follow.

State Legislation and Implications

Two enacted bills from the 1970 California Legislature have direct implications relating to the licensure of foreign medical graduates. The first of these, Assembly Bill 2427 (Duffy), only slightly bears upon foreign medical graduate licensure requirements, in that Board certification by an American specialty board (when such

training has been taken in the United States or Canada) may be substituted for required internship service without changing examination requirements.

Assembly Bill 37 (Lanterman), now Section 2193.7 of the California Medical Practice Act, has direct bearing on licensure for Guadalajara medical graduates who are U.S. citizens. This bill is best described by the Legislative Counsel's digest:

Requires a graduate of a medical school located in Mexico who at the time of his enrollment therein is a citizen of the United States, to take the same physicians and surgeons written examination given to graduates of California medical schools, to serve one year of post-graduate training in the field of family practice in an approved hospital, and to take the clinical and oral examinations given by the Board of Medical Examiners. Provides that upon successful completion thereof the individual shall receive a certificate as a physician and surgeon. Prohibits hospitals from requiring persons so qualified for postgraduate training to take examination other than written examination administered by a board as a condition of obtaining postgraduate training in such hospital.

The implications of this bill are obvious. First of all, if it is implemented as enacted, it is in direct confrontation with the concept of the ECFMG. In addition, similar bills could well be written which might involve the University of Bologna and the University of Rome. Specific areas that need resolution are possible loss of hospital accreditation, disaccreditation of AMA-approved graduate intern and residency programs, and a real threat to the very fiber of the ECFMG.

Because of potential conflicts resulting from a verbatim implementation of new Section 2193.7, a meeting involving interested parties was called by the California Medical Association in mid-November, 1971. It was made clear by Assemblyman Gordon Duffy that the legislative intent of AB 37 was to permit American students completing a four-year program in a Mexican medical school who had taken one year of general practice training and had passed the California written examination (FLEX) to be fully licensed as physicians and surgeons in California.

As a result of certain mutual understandings reached during a thoroughgoing discussion of

the issues involved, Assemblyman Duffy, a co-author of AB 37, agreed to introduce appropriate legislation to modify Section 2193.7 in the 1972 Legislature.

Essential (but not unanimous) accord was reached that U.S. citizens completing the four-year curriculum at a Mexican medical school (following acceptable premedical studies in the United States) would be issued a physician's and surgeon's certificate following (1) successful completion of one year of supervised clinical training approved by the Board of Medical Examiners in the field of general practice medicine and (2) successful completion of the same written examination normally given to graduates of California medical schools. (Representatives of the Board of Medical Examiners and several other individuals did not concur.)

It was understood that any such program of supervised clinical training would be under the direction of an approved medical school, and admission requirements to the program would be developed by the medical schools, to include suitable screening examinations. This year of supervised clinical training will not be creditable toward completion of an approved internship or as a year of approved residency training.

An annual report by the participating medical schools would be presented to the State Legislature, and the bill will expire after two years unless renewed.

The Board of Medical Examiners preferred to consider this year of special clinical training as a "clerkship" experience rather than a "state-approved internship," in order to permit the American graduate of a Mexican school to attain parity status only with graduates of domestic four-year medical school programs. Furthermore, it was the Board's position that licensure should be awarded only after an additional year of graduate training, which could consist of a classical internship or the first year of selected specialty training. Because of the special year of supervised clinical training, however, the Board did agree to omission of the usual oral and clinical examinations normally required upon completion of internship for U.S. citizens graduating from foreign medical schools (Section 2193.5).

It was suggested that initial support for the

program come from the contingent fund of the Board of Medical Examiners. The Board again demurred.

Modifications now under legislative draft (Assembly Bill 155) could permit easy entrance of the American graduate from Mexico to AMA-approved graduate programs. Following issuance of the physician's and surgeon's certificate upon successful completion of the year's clinical training and the FLEX examination, direct entrance into graduate programs is possible. An alternative for students who fail the FLEX examination would be through the new pathway, which also permits timing appropriate for the NIRM.P.

Lastly, it should be pointed out that there have already been certain licensure requirements withdrawn in several states, based on an Attorney-General's opinion that discrimination exists when differing licensure and educational requirements apply to U.S. nationals and foreign nationals.

Recommendations

A number of important points need to be considered by the California Medical Association, the California Board of Medical Examiners, the California Legislature, and the California medical schools. There is no question that the foreign medical graduate will be needed for the foreseeable future to provide sufficient skilled manpower for the health needs of the United States. Means must be sought to evaluate the quality of the foreign medical graduate experience as well as to expedite the licensure process and admission to postgraduate medical programs for qualified foreign medical graduates, citizens and non-citizens alike.

It is important to distinguish between U.S. nationals studying medicine abroad and citizens of other nations who are foreign medical graduates. The recent AMA position paper and most state board licensure requirements do discriminate on that basis. However, several states have modified their licensure requirements to ensure conformity regardless of citizenship status. This point must continue to be addressed by groups representing both national and state interests, and extreme care should be taken to avoid discriminatory practices based solely on citizenship or differential educational requirements.

From pre-1960 experience, the concept of the Educational Council on Foreign Medical Graduates and other "quality control" equivalents must be supported and maintained. The ECFMG has provided a vital national service which, if compromised, could induce chaos in an orderly assessment of the quality of education in the foreign medical graduate.

The California Medical Association and the State Board of Medical Examiners should consider changing the dates and other logistics of the written examinations for licensure in the state to better suit the purposes of foreign medical graduates. At present, the FLEX examination is administered in December and June, and successful passage of the written portion of this examination in June does not permit ready entrance into approved graduate programs without an excessive loss of time. Obviously, it is also near-impossible for such applicants to participate in the National Intern and Resident Matching Plan, and means should be sought for better articulation with that plan.

Because of the new AMA pathway to graduate medical educational programs and ultimate licensure, medical schools of the state should totally identify their medical applicant pool as "acceptable" or "non-acceptable." Not only would this permit the premedical experience of an individual to be certified, but also the fact that an entering position might not be available

in a California medical school would not keep a U.S. national from being eligible for federal scholarship support while attending a foreign medical school. With certified acceptability of credentials at this point, entrance via the new pathway to AMA-approved graduate programs and ultimate licensure would be facilitated.

In addition, the schools of medicine should accept the pedagogic challenge of developing suitable programs of supervised clinical training to make use of this new pathway.

Finally, the need for a continuing appreciation of the common goals and interests of organized medicine, the State Legislature, the Board of Medical Examiners, and the medical schools is self-evident. Only by truly cooperative efforts can the problems of the foreign medical graduate be best resolved.

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MELANOMA OF THE SCALP

In our series of melanomas of the head and neck, the most common site was the scalp. This is rather curious because melanoma of the scalp is ordinarily not diagnosed early. I think nearly all of us are guilty of not examining the scalp very carefully. It's very easy to examine the scalp on a bald man but it's rather difficult on some ladies who come in with special hairdos, hairpieces, and wigs, topped with a mucilaginous spray.

How many in this room have had their scalps examined? There's one, I see. That's a good illustration of what I am talking about. Everybody talks about looking at the nasopharynx or looking up the rectum, but nobody talks about the scalp.

—JOHN CONLEY, M.D., New York City
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Medical Economics

Free Clinics in California, 1971

A Socio-Economic Report of the Bureau of Research and Planning,
California Medical Association

THE EMERGENCE DURING THE LAST several years of a drug-oriented sub-culture in American society has influenced the development of a new kind of center for the delivery of health care services, the free clinic. During the summer of 1967, the Haight-Ashbury Free Clinic, under the direction of David Smith, M.D., opened its doors to San Francisco's "street people." Since that time, a number of similar clinics have been started; offering a wide variety of services their development is frequently referred to as the "free clinic movement."

The importance of this new phenomenon for the delivery of health care services to a selected population group in California suggested the need for more definitive data about the various clinics currently functioning. This *Socio-Economic Report* contains highlights of findings from a questionnaire survey conducted among all such clinics in June 1971. In addition to general information, it provides examples of four distinct types of free clinics found in California. The detailed report of findings will be published in the near future.*

Origin and Development of the Movement

Although free clinics began in recognition of the need for treatment of drug abuse and drug-related problems, they are no longer restricted to providing services to the drug-oriented, youth

sub-culture. In addition to this group, free clinics often provide care to the poor of all ages, minority persons, and others to whom the established systems of health care delivery are not readily available or who are unwilling or unable to seek care in traditional health care centers or through physicians in private practice.

Free clinics are each designed to meet the needs of a particular community and therefore, since community needs vary, so do the clinics. Because of this, there does not seem to be any one feature that categorizes a particular operation as a "free clinic." Jerome Schwarz of the Department of Preventive Medicine at West Virginia School of Medicine formulated the following as a working definition of a free clinic for a nationwide survey: "... a program which provides medical, dental, psychological or drug care without charges or red tape."¹ Excluded from his definition are in-residence and methadone programs, counseling by ministers, drop-in referral centers, and programs aimed at a defined population or a categorical disease.

The Southern California Council of Free Clinics in Los Angeles restricts the definition of a free clinic to a licensed, private, non-profit neighborhood health and social service center. Excluded are health centers operating under the sponsorship of a city or county government, or a federal agency. In both cases, the concept of a free clinic implies, in addition to small or no charges per patient visit, confidentiality, and as non-judgmental a climate as is possible in staff attitudes towards patients.

Reprint requests to: CMA Bureau of Research and Planning, 693 Sutter Street, San Francisco, Ca. 94102

*Included in this report will be a listing of all known free clinics throughout the state, detailed statistics on sponsorship, and sources of income and services provided, as well as the survey questionnaire used to compile the information.

Data about Clinics Compiled by
Questionnaire Survey

In June 1971 the Division of Socio-Economics and Research of the California Medical Association surveyed all 95 known clinics in California which seemed to fall into one of the above definitions of a free clinic. To date, 54 have responded; nine were excluded from the analysis because they do not provide any medical services at the clinic, but rather are "drop-in" referral centers, counseling centers, or in-residence treatment centers.

Of the 45 qualified respondents, 24 or approximately 53 percent are private, independent non-profit corporations. The Los Angeles County Health Department sponsors six clinics. Others are sponsored by private or community organizations, churches and neighborhood associations. One respondent, the American Indian Free Clinic, is sponsored by the Federal Economic and Youth Opportunities Agency. The Delta Health Project in Sacramento is sponsored by the Sacramento County Medical Association.

Sources of income for the free clinics vary considerably. Only three clinics, the American Indian Free Clinic, Delta Health Project and Long Beach Free Clinic receive any federal funds. Another ten are partially state funded and ten receive county funds. Other sources of income include community funds, group and individual donations, private foundation grants, fund raising events such as rock concerts, and street solicitations. One clinic, the Venice Community Family Health Center, has received financial assistance from the local district Los Angeles County Medical Association and from Area V of California Regional Medical Programs.

Most Clinics Located in Major
Metropolitan Areas

From the 45 responses it can be seen that free clinics function in at least 12 California counties. Los Angeles County alone accounted for 20 clinics, while San Francisco has seven. Responses were also received from four clinics in San Bernardino county, three each in Alameda and Orange counties, two in Riverside county, and one each in Mendocino, Monterey, Sacramento, San Mateo, Tulare and Ventura counties.

TABLE 1.—Age Distribution of Population Served at
34 Free Clinics

Age	Number	Percent
Under 15	4,000	12.7%
15-19	9,900	31.6
20-24	9,000	28.6
25-30	4,700	15.0
Over 30	3,800	12.1
Total	31,400	100.0

Age and Income Data for
Population Served

A total of 34 respondents indicated the average number of persons seen at the clinic each month and provided an estimate of age distribution of the population served. Table 1 shows the number and percent of the total 31,400 patients served each month by these clinics, according to age group. Approximately 75 percent of the persons seen at these clinics are between the ages of 15 and 30, while approximately 60 percent are between 15 and 24 years of age. Relatively few persons under 15 or over 30 are served at free clinics.

A total of 36 clinics provided estimates of the population served according to income levels. As might be expected, a high proportion of respondents (61 percent) reported that most or all of the population they serve are from families with lower income, that is, less than \$5,199. Only two clinics indicated that less than half of the population served were from lower income families and that 50 percent or more of the population were from higher income (\$7,600-\$10,500) families.

Broad Range of Service Provided

Table 2 lists the types of medical and other services provided at the 45 responding clinics, along with the number and percent of clinics offering each type of service. Services provided by over 75 percent of the responding clinics include general medical care, birth control, abortion counseling, laboratory work, treatment of venereal disease, health education, and job and family counseling. Although 60 percent of the clinics provide treatment for drug abuse, only three, or 6.7 percent of the total, have outpatient methadone programs.

TABLE 2.—*Services Provided at 45 Responding Free Clinics*

<i>Medical services</i>	<i>Number</i>	<i>Percent</i>	<i>Other services</i>	<i>Number</i>	<i>Percent</i>
General medical care	37	82.2%	Health education	37	82.2%
Emergency treatment	29	64.4	Drug education	31	68.9
Dental services	13	28.9	Tutoring	10	22.2
Eye examinations	14	31.1	Counseling (job, family)	38	84.1
Ear examinations	17	37.8	Paramedical training	15	33.3
Problem pregnancy care	24	53.3	Legal services	18	40.0
Pre-natal care	18	40.0	Youth social services	15	33.3
Well-baby care	16	35.6	Draft physicals	6	13.3
Treatment of venereal disease	35	77.8	"Rap" groups	29	64.4
Birth control services	36	80.0			
Abortion counseling	34	75.6			
Laboratory work	34	75.6			
Psychiatric services	27	60.0			
Surgical	6	13.3			
Treatment of drug abuse	27	60.0			
Outpatient methadone	3	6.7			
Detoxification	14	31.1			

Clinics Classified into Three Types

In his national survey of free clinics, Schwarz found that the clinics could generally be classified into three general types: neighborhood, "hippie," and youth. Neighborhood-type clinics are centers providing medical and/or dental care to families in areas where health services are not readily available. The population served is often from a particular minority group. Few neighborhood clinics offer treatment for problems relating to drug abuse. A hippie-type clinic, on the other hand, is one that provides some type of drug care (often including detoxification or rehabilitation) and serves many patients with drug-related illnesses. Youth-type clinics are also organized to give some drug care, although it is often limited to education and counseling. However, these clinics differ from hippie-type clinics in their sponsorship, having generally been developed and sponsored by adults, service clubs or other community groups concerned with problems of drug abuse among high-school students. These last two types of clinics also provide some types of general medical services.

Drug Abuse Treatment Centers Also Surveyed

These three types of clinics, as well as a fourth type, a center organized solely for the treatment of drug abuse, were included in the survey. The

fourth type, the drug abuse treatment center, generally does not provide any medical care services such as general medical care, emergency treatment unrelated to drugs, and treatment for venereal disease. Numerically, 17 of the respondents may be classified as neighborhood clinics, 15 as hippie clinics, 7 as youth clinics, and 6 as drug treatment centers. Although these classifications are not totally finite in terms of defining clinics, each seems generally more representative of one type than another and has been so classified.

Examples of Neighborhood Clinics

Two examples of neighborhood-type clinics are the Telegraph Hill Medical Clinic in San Francisco and the American Indian Free Clinic in Compton. The former serves the North Beach area of San Francisco, a community consisting largely of poor Chinese families. The clinic is staffed by one full-time and one part-time nurse and a part-time registrar who are paid by the city of San Francisco. Volunteer physicians include two pediatricians, two internists, an ophthalmologist, an orthopedist, a gynecologist and a dermatologist. It functions from 9.00 a.m. to 5:00 p.m., five days a week, to provide general medical care, emergency treatment, eye examinations, and light laboratory work. The city Department of Public Health utilizes the clinic

facilities once a week for well-baby care. In addition to these medical services, the clinic offers classes in health education, counseling services, youth social services and informal "rap" groups.

An estimated 340 individual persons are seen at the clinic each month; they average a total of 925 medical care visits. The majority of the population (94 percent) are from a lower economic group. Approximately 30 percent of the population served are under 15 years of age and 30 percent are over 30. The principal source of funding for the clinic is the City and County of San Francisco. If the patient can afford it, however, a minimum fee of \$1.00 is charged in order to help defray the clinic costs.

In January 1970 a group of Indians, with financial and technical assistance from Regional Medical Programs Area V, initiated the planning stages for the American Indian Free Clinic with the purpose of providing medical, dental, legal and other related services to anyone requesting them, but primarily to the estimated 60,000 American Indians of Los Angeles and surrounding communities. Three months later, under the direction of an all-Indian board of directors and an Indian administrator, the clinic began providing telephone information and referral services five afternoons a week by trained Indian aides. In October of the same year, the clinic facility was equipped and staffed to provide medical, dental, clinical and legal services two evenings a week. At present, approximately 300 persons are seen at the clinic each month; 250 of them seek medical care.

Approximately 50 percent of the population served by the clinic are under 15 years of age and 20 percent are over 30. The remaining 30 percent are approximately equally distributed within the 15 to 29 year age group. Half the population is estimated to be from families with incomes of less than \$5,199. Persons of moderate and higher income comprise 30 and 20 percent of the population, respectively.

Examples of "Hippie" Clinics

The Haight-Ashbury Free Clinic in San Francisco and Long Beach Free Clinic are two examples of Schwarz's hippie-type clinic. An important concern of each is the treatment of drug abuse and drug-related illnesses. Both clinics

are staffed to offer drug detoxification. The majority of the population served at each clinic is between the ages of 15 and 25.

The Haight-Ashbury Medical Clinic, the national pilot project for all free clinics, is sponsored by Youth Projects, Inc., a private, non-profit corporation. Primary sources of income for the clinic include funding from private foundation grants for education and research and patient donations.

Although originally developed to study and treat the abuses of psychedelic drugs, the health care needs of the population served demanded rapid expansion of the facilities and services provided. At present the clinic is divided into six separate sections: (1) medical care (including birth control and abortion counseling), (2) dentistry, (3) psychiatric care, (4) heroin detoxification, (5) treatment for drug abuse other than heroin, and (6) a publications department which periodically publishes *The Journal of Psychedelic Drugs*. Like all clinics surveyed, the Haight-Ashbury Free Clinic makes referrals to other health agencies, hospitals and voluntary agencies such as VD treatment centers.

The clinic is one of the largest in California, with an average of 3,000 client-visits per month. The professional staff includes one full-time and 30 part-time volunteer physicians. Other staff include over 100 nurses, psychologists, lay therapists, other paramedical personnel and community volunteers. Although some paramedical personnel are paid, most services are provided on a voluntary basis.

The Long Beach Free Clinic is the largest free clinic in Southern California, averaging 2,300 monthly visits by approximately 1,600 persons. Although no record is kept on the economic status of the population served, it is estimated that the majority are from families with lower income. Approximately 46 percent of persons seen are between the ages of 15 and 20 and 33 percent are between 21 and 24. Only 4 percent are under 15 years of age.

The Long Beach Free Clinic is currently organizing a medical advisory committee whose function will be to advise the medical director on policies, medical functions, and how to deal with problems in providing medical services. The Clinic draws from the services of approximately 60 volunteer physicians representing a

variety of specialties. Additionally, approximately 40 nurses, 50 to 60 other paramedical personnel and 300 community workers volunteer their services to the clinic on a part-time basis.

Besides regular medical, dental and psychiatric services, the clinic has an extensive drug abuse program. In January 1969 the clinic became the first facility in Los Angeles County to do outpatient heroin detoxification and in January 1971, the first non-government facility in Southern California to do outpatient barbiturate detoxification. Detoxification includes physician prescribed non-narcotic medication and psychiatric crisis and group counseling as well as certain social services. The clinic also offers counseling and medical services for amphetamine and psychedelic drug abusers.

Examples of Youth Clinics

Two examples of youth-type free clinics are the Youth Service Center of Riverside, Inc. and the Van Nuys Youth Clinic.

The Van Nuys Youth Clinic is one of five respondents sponsored by the Los Angeles County Health Department. The other four include Hawaiian Gardens Youth Clinic, Santa Fe Springs Youth Clinic, Northeast Health Center and Southeast Health Center. Each clinic has a clinic coordinator or administrator who functions under the health department's Youth Clinics Medical Director.

Approximately 1,700 persons are seen at Van Nuys Youth Clinic each month. Approximately 80 percent are between the ages of 15 and 25, with just 5 percent under 15 years of age. It is interesting to note that 75 percent of persons served are from higher income families and only 5 percent are from the lowest income group. This is not the case, however, in three of the other Los Angeles County youth clinics responding to the survey, (Hawaiian Gardens, Northeast and Southeast), where low income persons comprise between 70 and 100 percent of the population served. Statistics on socioeconomic background are not available for Santa Fe Springs Youth Clinic.

The volunteer staff of Van Nuys Youth Clinic includes nine therapists, six community workers and five social workers. Nine physicians, two nurses, two psychologists, one social worker, one

health director, one nutritionist, and one laboratory technician are reimbursed for their services on an hourly basis.

Youth Service Center of Riverside, Inc., is a private, non-profit corporation. Funding for the center comes from a variety of sources including United Fund, Junior League, and the California Council on Criminal Justice. The center also has a contract with the Riverside Unified School District to teach remedial reading skills to high-school students. A part-time medical director and a medical advisory committee meets informally on an "as needed" basis. The committee also acts as liaison with the Riverside County Medical Association, which has endorsed the clinic.

With the exception of one person who is paid on an hourly basis to keep accurate inventory of equipment and supplies, all persons providing services at the center are volunteers. Professional volunteers include approximately 25 physicians, 25 nurses and five psychologists. The center has over 200 community volunteers, including 95 remedial reading instructors and other paraprofessionals trained at the center. In addition to regular medical services, psychiatric and legal services, the center offers a summer camping program and an older brother-sister program. All services are free, voluntary and confidential.

One Example of a Drug Clinic

Although not always referred to as free clinics, drug-type clinics were included in the survey because of the many common goals and interests they share with free clinics, such as concern for young alienated members of society. Frequently, services offered by drug treatment centers include all those of the free clinics with the exception of general medical care and dental care. One such organization that is philosophically and organizationally very similar to the hippie-type free clinic is Do It Now Foundation in Hollywood. This is a national, educational foundation, supported through the sales of printed and other types of education material about drugs. The foundation in Hollywood has a medical director on call 24 hours a day and a medical advisory committee on research and treatment of drug-induced medical problems.

The staff of the center includes one physician in community medicine and 30 interns and resi-

dents from the University of Southern California Medical Center, two psychologists, five lay therapists, 15 paramedical personnel with extensive drug experience and six community volunteers. All services provided at the center relate to the use of drugs. General medical care for drug-related illnesses and emergency treatment for drug overdose is provided. Laboratory analysis of drugs, drug counseling and encounters, and detoxification are also provided at the center. The foundation is currently developing an outpatient methadone program. Other services include some types of health education, extensive drug education, paramedical training, legal services and suicide prevention.

Publications of the Foundation include pamphlets discussing the abuses of various kinds of drugs such as amphetamines, barbiturates, heroin, and speed; a cartoon publication developed especially for ages 8 through 12 as an effective approach to preventive drug education; and educational, peer-oriented record album with music by contemporary, well known musicians; and a special packet of educational material for teachers, counselors and administrators. The foundation also publishes a newspaper containing peer-group facts and news about drugs.

Coordination Can Prevent Wasted Energies

The primary goal of all free clinics is to provide patients with quality health care and related services. Since the movement began, however, clinics have had to face continual crisis situations in funding, staffing and community relations. With each clinic struggling to maintain its own existence, problems may also arise between clinics—such as competition for community support, geographic location and overlapping services. In 1970 the free clinics in Southern California developed a council of free clinics to aid in solving some of their shared problems. Of prime importance to the council was the preservation of each individual clinic's independence and individuality.

The Southern California Council of Free Clinics (SCCFC) consists of a board of directors composed of a representative from each of 22 member clinics and an advisory board whose function is to assist and advise the council in areas such as comprehensive health planning,

fund raising, public relations and legal affairs. SCCFC has received financial support from Regional Medical Programs Area V and the Economic and Youth Opportunities Agency of Greater Los Angeles.

Relationships with Medical Societies

Among the goals of SCCFC is furthering the acceptability and cooperation of the medical and general communities. Survey respondents were asked whether they had sought the advice or assistance of their county medical society. Of the 45 respondents, 27 (60 percent) had done so. The types of assistance and cooperation free clinics would like the medical community to provide is reflected in their comments.

Three responding clinics have received some assistance or have been endorsed by their local medical societies. One, the Delta Health Project, is sponsored by the Sacramento County Medical Society. As mentioned above, Venice Community Family Health Center is partially funded by the local medical society. A spokesman for the Youth Service Center of Riverside stated, "We are proud to be endorsed by the Riverside County Medical Association and enjoy a good level of communication with their officers." Two other clinics reported that they have occasionally contacted local medical societies for referral purposes or for volunteer physicians or supplies.

The remaining 15 respondents who commented on this question indicated that medical societies are reluctant to support free clinic facilities. One respondent attributed this reluctance to a lack of knowledge or misconceptions of the extent of the problems and goals of the free clinics. The willingness of most free clinics to provide the California Medical Association with information concerning themselves suggests their desire to acquaint members of organized medicine with the problems and needs of the free clinic community. Their responses to the survey also seem to indicate that some free clinics are not merely willing to accept, but may actively welcome, assistance from the medical community as it is represented by county and state medical societies.

REFERENCE

1. Schwarz JL: Free health clinics: What are they? *Health Rights News* 4:5, Jan 1971

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PUBLIC HEALTH REPORT

Frederick B. Hodges, M.D., Chief Deputy Director, State Department of Public Health

Proficiency Testing For Physicians' Office Laboratories

A RECENT CHANGE IN THE Business and Professions Code (Section 1241), effective March 4, 1972, requires physicians' unlicensed office laboratories to participate in proficiency testing, a procedure which shows how performance compares with that of reference or peer laboratories. The California legislature passed this law in 1970, and it was amended in 1971. The State Department of Public Health and the California Medical Association cooperated in framing policies and regulations to implement it. The Department, the CMA and representatives of various medical specialties have agreed upon the following testing program.

Since it is impractical or impossible to test all procedures which are carried out in a clinical laboratory, a representative group of tests was selected to fulfill the requirements of the law. Physicians who perform the following tests in their laboratories are subject to proficiency testing requirements:

Hematology

Hemoglobin
Hematocrit
Prothrombin time
Differential smear

Non-syphilis Serology

Antistreptolysin-O
Heterophile
Blood agglutination
Rheumatoid arthritis

Microbiology

Bacteriological
identification
Parasitological
identification

Chemistry

Glucose
Urea nitrogen
Uric acid
Cholesterol
Calcium
Sodium
Potassium

Syphilis Serology

VDRL
ART
FTA-ABS
AFTA
RPR (circle)
card

Immunohematology

Blood grouping
Rh typing
Irreg. antibody
detection

A laboratory which does not perform these tests is not subject to proficiency testing requirements, nor is testing required for urinalysis.

The following tests, which are performed as screening procedures or with such limited application that neither testing services nor the Department can evaluate performance, need not be proficiency tested.

Throat cultures
Gonococci cultures
Urine cultures

} If organism not specifically isolated or identified

Cellulose tape test
for pinworm

Hemoglobin
Hematocrit

} If not performed in conjunction with any other test being proficiency tested

However, the Department recommended that the physician voluntarily enroll in a testing program in order to maintain a high quality of test performance in all laboratory areas.

Four societies that operate proficiency testing programs have been approved by this Department to provide these services to office laboratories as well as to licensed clinical laboratories in California. These approved testing services are:

American Association of Bioanalysts
Proficiency Testing Service
105 West Elizabeth Street, Suite 107
Brownsville, Texas 78520
Telephone (512) 546-5315

College of American Pathologists
Quality Evaluation Programs
230 North Michigan Avenue
Chicago, Illinois 60601
Telephone (312) 346-9150

California Society of Internal Medicine
(CSIM)
Proficiency Testing Service
703 Market Street, Room 1412
San Francisco, California 94103
Telephone (415) 362-1548

College of American Pathologists
American Society of Internal Medicine
Proficiency Evaluation Programs
230 North Michigan Avenue
Chicago, Illinois 60601
Telephone (312) 346-9150

Such services consist of mailing test materials to each subscribing laboratory four times a year, evaluating results reported by the laboratory and returning to the subscriber a report which indicates how well his results compare with those reported by his peers (or selected reference laboratories) as "correct."

Three professional societies in California will assist laboratories in evaluating their proficiency test results and providing any consultation physicians need. Physicians may request help from the Department or directly from the California Association of Bioanalysts, the California Society of Internal Medicine, or the California Society of Pathology.

When performance difficulties in a procedure are encountered, the Department or the society will alert the laboratory and offer assistance. If the problems persist over four consecutive quarters, the Department will ask the laboratory to discontinue its service with that test procedure in the best interests of public health.

Since the first quarter of the year has already passed, physicians may now subscribe to a testing service for only two or three quarters of 1972, with prorating of annual fees. The proficiency testing services will provide information about procedures which can be evaluated, different types of testing programs offered and costs, from which the physician can choose the kind of service most appropriate to his needs.

Does proficiency testing improve laboratory performance? The Department's experience with licensed laboratories, all of which must be proficiency tested in 1972, suggests that test performance greatly improves if laboratories respond to proficiency test results by taking appropriate action. Published and documented studies elsewhere in the nation, some of them national in scope, support this conclusion, as do studies carried out by the California Society of Pathologists and the California Society of Internal Medicine.

California has set an example to the nation as the only state which has ever set what are believed to be appropriate standards for physicians' office laboratories. The current law is part of a long-term effort to maintain high performance standards in *all* the laboratories serving medical practitioners in this state, an effort in which California's physicians have participated for several decades.

MORNING STIFFNESS AS A SYMPTOM

A frequent systemic manifestation of rheumatoid arthritis is morning jelling or stiffness. This occurs commonly in joints that are overtly involved with the disease process but also occurs in areas where there is no obvious joint disease. Patients are stiff all over. This is pronounced on getting out of bed and it stays for a long time. If it disappears in the first walk to the bathroom, that is not what we are talking about. It's not a 15-minute type of thing. It's more like a half hour or three-quarters of an hour. The patient can usually tell you when this morning stiffness sensation has improved to the point where no further improvement can be expected. This is a good index of disease activity. It is also very pertinent to the diagnosis of rheumatoid arthritis.

—JOHN L. DECKER, M.D., Bethesda
Extracted from *Audio-Digest Internal Medicine*, Vol. 18, No. 2, in the Audio-Digest Foundation's subscription series of tape-recorded programs. For subscription information: 1930 Wilshire Blvd., Suite 700, Los Angeles, Ca. 90057

In Memoriam

Persons wishing to do so may make contributions to the Physicians' Benevolence Fund to honor the memory of a member who has died. Members of the family will be notified that such a contribution has been made and the name of the donor will be supplied.

Checks should be addressed to Physicians' Benevolence Fund, Inc., California Medical Association, 693 Sutter Street, San Francisco, Ca. 94102.

BERNSTEIN, DONALD EARL, San Francisco. Died February 28, 1972 in San Francisco, aged 55. Graduate of Stanford University School of Medicine, Palo Alto-San Francisco, 1947. Licensed in California in 1947. Doctor Bernstein was a member of the San Francisco Medical Society.

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*

BLATHERWICK, NORMAN H., Los Angeles. Died February 6, 1972 in Los Angeles of myocardial infarction, aged 58. Graduate of the University of Southern California School of Medicine, Los Angeles, 1939. Licensed in California in 1939. Doctor Blatherwick was a member of the Los Angeles County Medical Association.

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*

CASEY, EARLE ADDISON, Oakland. Died February 7, 1972 in Oakland of heart disease, aged 64. Graduate of the University of Oklahoma School of Medicine, Oklahoma City, 1935. Licensed in California in 1936. Doctor Casey was a member of the Alameda-Contra Costa Medical Association.

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*

CHENEY, MARSHALL CHIPMAN, Berkeley. Died February 16, 1972 in Berkeley of metastatic cancer of the colon, aged 83. Graduate of Harvard Medical School, Boston, 1918. Licensed in California in 1919. Doctor Cheney was a member of the Alameda-Contra Costa Medical Association.

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DOOLEY, JAMES HENRY, Paso Robles. Died January 12, 1972, aged 52. Graduate of the New York University College of Medicine, 1945. Licensed in California in 1953. Doctor Dooley was an associate member of the San Luis Obispo County Medical Society.

EDMEADES, DONALD T., Los Angeles. Died February 27, 1972, aged 58. Graduate of Columbia University College of Physicians and Surgeons, New York, 1939. Licensed in California in 1940. Doctor Edmeades was a member of the Los Angeles County Medical Association.

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*

LONG, JAMES CLIFFORD, San Francisco. Died March 2, 1972 in San Francisco, aged 76. Graduate of the Creighton University School of Medicine, Omaha, 1924. Licensed in California in 1924. Doctor Long was a member of the San Francisco Medical Society.

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*

RICKETTS, FREDERICK JASPER, El Cajon. Died February 3, 1972, aged 59. Graduate of the University of Illinois College of Medicine, Chicago, 1936. Licensed in California in 1953. Doctor Ricketts was a member of the San Diego County Medical Society.

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*

SMYTH, FRANCIS SCOTT, SR., San Francisco. Died February 6, 1972 in San Mateo, aged 76. Graduate of the University of California Medical School, Berkeley-San Francisco, 1922. Licensed in California in 1922. Doctor Scott was a retired member of the San Francisco Medical Society and the California Medical Association, and an associate member of the American Medical Association.

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*

STUDEBAKER, LELAND F., Los Gatos. Died December 24, 1971 in Redwood City, aged 63. Graduate of Stanford University School of Medicine, Palo Alto-San Francisco, 1935. Licensed in California in 1937. Doctor Studebaker was a member of the Santa Clara County Medical Society.

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TURKEL, HENRY WILLIAM, San Francisco. Died February 26, 1972 in San Francisco of heart disease, aged 56. Graduate of the University of California Medical School, Berkeley-San Francisco, 1943. Licensed in California in 1944. Doctor Turkel was an associate member of the San Francisco Medical Society.

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*

WATKINS, ROBERT PRESTON, San Francisco. Died March 4, 1972 in San Francisco of heart disease, aged 63. Graduate of Stanford University School of Medicine, Palo Alto-San Francisco, 1935. Licensed in California in 1939. Doctor Watkins was a member of the San Francisco Medical Society.

BOOK REVIEWS

CALIFORNIA MEDICINE does not review all books sent to it by the publishers. A list of new books received is carried in the Advertising Section.

CLINICAL DISORDERS OF IRON METABOLISM—2nd Edition, Revised and Expanded—Virgil F. Fairbanks, M.D., Consultant, Department of Clinical Pathology, Mayo Clinic; Assistant Professor of Medicine, Mayo Graduate School of Medicine (University of Minnesota), Rochester; John L. Fahey, M.D., Senior Physician, Department of Hematology, Division of Medicine, City of Hope Medical Center, Duarte, Ca.; Ernest Beutler, M.D., Chairman, Division of Medicine, and Director, Department of Hematology, City of Hope Medical Center, Duarte, Ca.; Clinical Professor of Medicine, University of Southern California, Los Angeles. Grune & Stratton, Inc., 111 Fifth Avenue, New York City (10003), 1971. 486 pages, \$25.00.

The need for an updated, comprehensive monograph of iron metabolism and associated disease states is readily apparent to anyone in the field of hematology and fortunately this need has been excellently filled with the second edition of this book. The basic format is retained in this edition but all of the chapters have been extensively revised and appropriately lengthened. Emphasis is on more recent publications and this is reflected in the bibliography where 40 percent of the more than 1700 references were published in the eight-year interval between editions. A completely new chapter on sideroblastic anemias has been added. Other chapter titles include iron metabolism, iron deficiency, therapy of iron deficiency, acute iron poisoning, and hemochromatosis. In addition there is an enjoyable chapter on the history of iron in medicine and a rather unique chapter on the syndromes of iron deficient states. Many poorly understood and infrequently well-documented syndromes thought to be related to iron deficient states are discussed in considerable detail.

Taken as a whole, or by individual topics, this book has encyclopedic scope covering, in depth, every facet of iron metabolism. It is clinically oriented containing very practical, clinical information not readily found in other sources and hence is of value to students, residents as well as the practicing physician. For the specialist, this concisely written monograph helps put very conflicting and confusing data, whether old or new, into proper perspective. There are no vague generalities. In some areas where definitive information is lacking, the available data are presented and an editorial objectiveness is maintained.

This fine monograph is recommended to anyone engaged in medical practice or research and to others interested in iron metabolism and related disease states.

THOMPSON ADAMS, M.D.

* * *

MANAGEMENT OF JUVENILE DIABETES MELLITUS—2nd Ed.—Howard S. Traisman, M.D., F.A.A.P., Associate Professor of Pediatrics, Northwestern University Medical School; Associate Attending Physician, Division of Endocrinology, and Head of the Diabetes Clinic, Children's Memorial Hospital; Associate Attending Physician, Chicago Wesley Memorial Hospital, Chicago; Attending Physician, Evanston Hospital, Evanston, Illinois. The C. V. Mosby Company, 3207 Washington Blvd., St. Louis, Mo. (63103), 1971. 223 pages, \$19.75.

The challenge with its reward and the frustration with its failure have confronted every physician involved with the management of diabetes mellitus in a young person.

For those who are met with this difficult problem occasionally, a detailed practical approach is needed. This edition meets this need and also blends the concerned approach of a pediatrician who really understands his patient's plight.

The orientation of this book is clinical. The discussion of recent research developments in diabetes (including a chapter on pancreatic transplants) is superficial but adequate. In addition the section on the pathogenesis of diabetes mellitus is unique. Doctor Traisman reveals his deep regard for the importance of diet and dietary instruction by devoting 41 pages to this subject. He includes detailed copies of requisition forms for regular weighed diets, diets for sick days and food tables. These forms and tables leave little to imagination.

The important facets of instruction in the care and understanding of diabetes for the patient and his family is stressed in a chapter which includes information about available educational material, famous diabetics, urine testing, insulin administration, use of glucagon, and what the teacher should know about the diabetic student. Dr. Traisman has included in the appendix "Instructions for students and graduate nurses on routine nursing care of juvenile diabetic patients," instructions on collection of specimens for diabetic urinary tests and instructions to parents of the diabetic child. In this same appendix fluid and electrotype therapy is outlined along with a listing of available sugarless drug preparations.

This book is an excellent guide for the pediatrician and generalist for whom it was designed. My own satisfaction in reviewing this book was to discover a pediatrician whose belief in the importance of carefully controlling blood sugar agreed with my own.

CHARLES H. BRINEGAR, JR., M.D.

* * *

PROGRESS IN NEUROLOGY AND PSYCHIATRY—Volume XXV—Edited by E. A. Spiegel, M.D., Dr. Med. (Hon.), Emeritus Professor and Head of the Department of Experimental Neurology, Temple University School of Medicine, Philadelphia. Grune and Stratton, Inc., 757 Third Avenue, New York, N.Y. (10017), 1970. 495 pages, \$28.75.

This volume consists of a series of reviews of the literature of 1969 in the broad areas of Neurology, Neurosurgery and Psychiatry. Neurology is subdivided into Clinical Neurology, Otoneurology, Epilepsy, the Autonomic Nervous System, etc. The reviews, as such, are really annotated bibliographies and are relatively uncritical in both choice of articles as well as the encapsulated conclusions given for each citation.

The Progress in Neurology and Psychiatry volumes are most useful as a ready source of current bibliographical material; physicians in search of a current reference to a psychological or neurological disorder would do well to have access to them.

NEIL H. RASKIN, M.D.



Human Diseases Associated with Mycoplasmas

With an Appendix on Simple Culture Techniques

HERBERT J. HARWICK, M.D., GEORGE M. KALMANSON, M.D.
AND LUCIEN B. GUZE, M.D., Los Angeles

■ *The mycoplasmas (formerly called pleuropneumonia-like organisms, or PPLO) are a group of pleomorphic micro-organisms characterized by lack of cell wall and ability to form colonies on agar resembling tiny fried eggs. They have been recognized as pathogens of lower mammals since 1898. Of the more than 40 known veterinary species, many are pathogens, commonly causing pneumonia, arthritis or arteritis. Of the mycoplasmas found in man, Mycoplasma pneumoniae is the only well established human pathogen. It is responsible for a variety of respiratory syndromes, of which the most frequently recognized is cold agglutinin-positive atypical pneumonia. Hematologic, neurologic and dermatologic complications of this infection have been noted. M. hominis has been implicated as a causative factor in various febrile complications of pregnancy, such as septic abortion and amnionitis. T-strain mycoplasmas are ubiquitous in the human genitourinary tract, but attempts to link their presence to disease have thus far been unsuccessful. Mycoplasmas also have been associated with neoplastic disease and with rheumatoid arthritis. The validity of these latter findings is unclear, and additional study is needed.*

MYCOPLASMA IS THE GENERIC NAME assigned in 1954 to the micro-organisms previously called pleuropneumonia-like organisms. The first member of this group was isolated in 1898 by Nocard

From Research and Medical Service, Wadsworth Veterans Administration Hospital, Los Angeles, Department of Medicine, Harbor General Hospital, Torrance, and Department of Medicine, University of California, Los Angeles.

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Submitted June 21, 1971.

Reprint requests to H. J. Harwick, M.D., Research and Medical Service, Wadsworth Veterans Administration Hospital, Wilshire and Sawtelle Boulevards, Los Angeles, Ca. 90073.

et al¹ and was proved to cause epidemic bovine pleuropneumonia, a disease which decimated herds of cattle in Western Europe during the latter half of the nineteenth century. By 1910, the microscopic morphologic features of the organisms had been described.² Despite their propagation in cell-free broth, they were considered viruses until the early 1930's, when they were shown to form very small colonies on serum-containing agar.³ Due to dense growth in

the center and light growth at the periphery these colonies appeared under the microscope as small fried eggs. This colonial morphologic feature has become a hallmark of the mycoplasmas (Figure 1).

Confusion arose in 1935, when Klieneberger⁴ observed "fried egg" colonies in a culture of the bacterium *Streptobacillus moniliformis* (a cause of rat-bite fever). In honor of the Lister Institute, the term L-form* was applied to all such organisms.

Until recently, the relationship between L-forms and mycoplasmas has been controversial. Sophisticated techniques of nucleic acid analysis have now suggested that mycoplasmas are a genetically distinct group of micro-organisms.^{5,6}

Mycoplasmas do not have a cell wall. Electron micrographs show them to be extremely pleomorphic organisms bounded by a three-layer unit membrane. They are about the same size as the large viruses, with the smallest reproductive units the size of the myxoviruses (about 125 millimicrons).⁷

Much of our knowledge of mycoplasmas derives from study of infections in lower mammals. At least 40 species have been isolated, many of which are pathogenic for one or more animal hosts. A sampling of veterinary diseases caused by mycoplasmas would include pneumonia and pericarditis in cattle,¹ goats⁸ and rodents;⁹ purulent or chronic relapsing arthritis in swine,¹⁰ rodents¹¹ and fowl;¹² arteritis in turkeys¹³ and encephalitis in mice.¹⁴ Recently, mycoplasmas have been associated with an increasing number of plant diseases; several apparently respond to tetracycline therapy.¹⁵

Pathogenicity in man was first suggested by the isolation of a mycoplasma in pure culture from a Bartholin's gland abscess in 1937.¹⁶ Since then, seven distinct species and another group of biologically similar but as yet unclassified organisms (the "T" strains) have been isolated regularly from man.¹⁷ Of these, *Mycoplasma pneumoniae*, a common respiratory pathogen, has satisfied Koch's postulates; the status of the T-strains, which are found in the genitourinary tract, is uncertain; and *M. hominis* appears to be an opportunistic genital pathogen. Of the remainder, *M. salivarium* is frequently found in saliva and gingival scrapings and *M. orale* 1 is a



Figure 1.—Typical fried-egg colony produced on agar by mycoplasmas (magnification X20).

common inhabitant of the oropharynx; *M. orale* 2 and 3 are less common inhabitants of the oropharynx, and *M. fermentans*, though rarely isolated, can be found in either the respiratory or genital tracts. Several animal species also have been recovered from human specimens inoculated into various tissue culture systems. The validity of these isolations is in doubt due to the high rate of tissue culture contamination by mycoplasmas.¹⁸

Mycoplasma pneumoniae

Atypical pneumonia was noted as an entity distinct from pneumococcal (typical) pneumonia in 1938,¹⁹ but the disease did not assume major importance until World War II. During the early 1940's, epidemics recurred in Armed Forces training centers. Though these epidemics were characterized by low mortality, the two- to three-week duration of illness disrupted training schedules.

In 1941, Peterson, Ham and Finland²⁰ identified the presence of cold agglutinins in convalescent sera from approximately 50 percent of patients with this syndrome. As a group, the cold agglutinin-positive patients tended to have a more prolonged course. Their filtered, bacteriologically sterile sputum was shown to transmit disease to human volunteers.²¹ Further work by Eaton, et al established that the agent could be passed to certain rodents²² and could be propagated in chick embryo. Liu later demonstrated discrete particulate bodies localized in chick embryo bronchial epithelium;²³ and, in 1961, Marmion and Goodburn suggested that the organism

*Subsequently, others have used such terms as *protoplast*, *spheroplast*, *L-phase growth* and *atypical bacterial variant* to describe cell wall defective organisms derived from a variety of bacterial species.

might be a mycoplasma rather than a virus.²⁴ One year later, the organism was grown in a cell-free medium by Chanock, Hayflick and Barile²⁵ and was named *Mycoplasma pneumoniae*. The artificially cultivated organism has been shown by serological methods to be identical to Eaton's agent and to produce the identical disease in human volunteers.^{25,26}

The course of infection by *M. pneumoniae* is variable, ranging from subclinical through bronchopneumonia to rare cases of lobar pneumonia with effusion.¹⁷ In most cases the disease begins with a prodrome of malaise and upper respiratory symptoms. Severe headache is often a prominent complaint.²⁷ Shortly after onset a persistent cough which may be productive of small amounts of sputum usually develops. Fever between 38.1° and 38.9° C (100.8° and 102° F) is usual, but the patient's malaise is often greatly out of proportion to the degree of fever. Arthralgias, nausea or vomiting may also be noted. Careful physical examination may disclose only a few rhonchi with fine râles over the posterior mid-lung fields. Radiographically, extensive infiltration—more than would be anticipated from the localized physical findings—may be seen. The superior segment of the lower lobe is involved most frequently. In about 20 percent of some series, the infiltrate is bilateral; occasionally a small pleural effusion may be found.^{28,28a}

The leukocyte count is usually normal or mildly elevated with an essentially normal differential. Cold agglutinins are usually not found in the first few days of illness, but if the patient is seen later in the course of the illness they may be present. By the end of the third week, 40 to 80 percent of patients will have elevated cold agglutinins,* and 80 to 90 percent of patients will have an elevated complement fixation titer to *M. pneumoniae*. On admission, the Coombs test may be positive, especially in the presence of cold agglutinins.²⁹ Though the organism usually takes from two to three weeks to grow on primary isolation, culturing of material from the oropharynx or sputum is relatively simple and should be done where possible for epidemiological reasons (see appendix). Culture combined with serologic methods should identify close to 100 percent of cases.

M. pneumoniae epidemics are characterized by their slow spread with an incubation period

between contacts of about three weeks.³⁰ The incidence rate of *M. pneumoniae* infection is highest among adolescents and young adults. Myringitis may occur but is more common in children.³¹ Primary atypical pneumonia can affect patients of any age; but, in children below six years and adults between 45 and 70 the disease is rare.^{31,32}

Although year to year incidence of *M. pneumoniae* infection may vary widely in different geographic locations, the seasonal incidence in the general population is fairly uniform.³³ Thus, in winter, when bacterial pneumonia is more common, *M. pneumoniae* causes a smaller proportion of disease than it does in the summer when overall rates of pneumonia are low.

The total course of the untreated pneumonia is usually about three weeks, with fever persisting for five to seven days and the radiographic infiltrate visible for two to three weeks. On occasion, malaise and cough may be present for as long as two months.³³

With exception of an occasional case of pericarditis,³⁴ complications of *M. pneumoniae* infection are rare. Bacterial superinfection is unusual.³³ Several cases of fatal hemolytic anemia have been reported in association with high titers of cold agglutinins,³⁵ and Feizi suggested *M. pneumoniae* infection may be the initial trigger in some cases of chronic "autoimmune" hemolytic anemia.²⁹ Renal failure in association with high cold agglutinin levels has also been reported.³⁶ Neurological complications of *M. pneumoniae* infection can be quite varied. Encephalitis, meningo-encephalitis,³⁷ transverse myelitis and Guillain-Barré syndrome³⁸ all have been seen in patients with atypical pneumonia from whom either *M. pneumoniae* was isolated or in whom serological evidence of infection was demonstrated. Several cases of each have also been reported in patients with no antecedent history of respiratory ailment, but with serological evidence of recent *M. pneumoniae* infection. Most of the encephalitis cases reported have been self-limited, but deaths have occurred in patients with Guillain-Barré syndrome and transverse myelitis.

Erythema multiforme minor and exudativum (Stevens-Johnson syndrome)³⁹ both have been associated with *M. pneumoniae* respiratory infection, and the organism itself has been cultured from blister fluid.⁴⁰ Petechial and macular eruptions also have been noted, but these have been

*Though adenovirus pneumonia may also be cold agglutinin-positive, this infection is uncommon in civilian population groups.

transient and of little apparent importance.²⁸ The erythema multiforme syndromes are significant because of the discomfort they cause and the possibility of serious superinfection. It is unlikely that *M. pneumoniae* infection causes all Stevens-Johnson-like illness, but the true extent of the association has not been determined. Whether antibiotic therapy of the antecedent respiratory infection will prevent complicating neurological, hematological or dermatological illness is not known.

Three antibiotics have been shown to lessen the morbidity associated with *M. pneumoniae* infection and to speed resolution of the pulmonary infiltration. These are tetracycline, erythromycin and demethylchlortetracycline.^{41,42} Penicillin or penicillin-like drugs have no antimycoplasmal activity because these organisms lack a cell wall. Each of the three drugs is equally effective in treating the clinical illness, and choice of antibiotic should be based on patient tolerance. Therapy may be discontinued 48 to 72 hours after the patient has become afebrile. Although erythromycin is the most active against the organism *in vitro*, tetracycline has been found to be slightly more effective in reducing spread of infection to susceptible contacts; but, as is the case with each of these antibiotics, the organism can still be isolated from the oropharynx of 15 to 20 percent of patients for as long as three months after clinical recovery.⁴²

Although *M. pneumoniae* infection usually cannot be differentiated prospectively from viral pneumonitides, the reduction of morbidity in mycoplasmal disease by antibiotics is sufficient to warrant a recommendation that patients presenting with atypical pneumonia probably should be treated. A sputum smear and other appropriate studies must always be performed to rule out bacterial infection. Penicillin is still the drug of choice for pneumococcal pneumonia.

T-Strain Mycoplasmas

T-strain mycoplasmas were described by Shepard in 1954.⁴³ These organisms are distinguished by the tiny colonies they form on agar (approximately 10 μ to 15 μ in diameter) and by their requirement for urea as an energy source.⁴⁴ During the past decade, they have been implicated as a cause of non-gonococcal urethritis, post-gonococcal urethritis, female infertility, abortion,

"abacterial pyelonephritis" and other obscure diseases of the genitourinary tract. Teleologically, their metabolic requirement for urea makes the T-strains an ideal hypothetical candidate to cause almost any genitourinary disease of an unknown, but possibly infectious, nature. Recently improved cultural techniques have shown their ubiquity in the lower genitourinary tract, to the extent that Braun et al⁴⁵ have reported isolation of T-strains from the urine or vagina of 79 percent of women on their initial visit to a routine prenatal clinic. Further, several investigations performed in England comparing isolation rates from urethral swabs in normals to those in patients (male or female) with gonococcal urethritis, non-gonococcal urethritis, post-gonococcal urethritis, trichomonas vaginitis or urethritis and other "non-specific" genital infection have shown no significant differences between any of these groups.^{46,47,48} Although Braude showed bladder stone formation in rats after intrarenal injection of T-strains,⁴⁹ the organisms have not been isolated from the upper urinary tract of man or animal. Furthermore, no simple serological test for evidence of infection is available to help delineate a pathogenic role for these organisms. Despite these problems, a group of investigators in Boston recently noted the birth weight of infants from Negro mothers who had cultures positive for T-strains before delivery was significantly lower than that of infants from mothers from whom no mycoplasmas were isolated.⁵⁰ Whether these data represent cause, effect, or a chance association with other interrelated factors is not yet known.

Mycoplasma hominis

Although T-strains and *M. hominis* are often found together, evidence that *M. hominis* might be a human pathogen is stronger than for T-strains. Three tests for serological response to *M. hominis* are available: complement fixation, indirect hemagglutination and metabolism inhibition. Each of these has been applied to broad population groups with somewhat similar results. In women, antibody begins to appear with puberty; and titers increase steadily through the reproductive years to peak in the fifth decade and then fall after age 50. In men, antibody also appears with puberty but rises to lower levels than in women, increasing steadily with age to the seventh decade. Comparing matched age groups

and sexes, titers to *M. hominis* are higher in groups with increased sexual promiscuity and low socio-economic status.⁵¹

These data have suggested that *M. hominis* might be involved in (1) venereal diseases, (2) infectious complications of the reproductive system in women and (3) in urinary tract problems of older men. No convincing evidence has been marshalled to support propositions one or three, but proposition two has been a more fruitful pursuit: *M. hominis* has been isolated from Bartholin's gland abscesses,¹⁶ ovarian abscesses and blood cultures of women with ovarian abscesses,⁵² blood cultures taken during fever appearing after therapeutic abortion,⁵³ blood cultures taken during spontaneous septic abortion,⁵⁴ blood cultures taken during postpartum fever,^{55,56,57} amniotic fluid following vaginal examination, internal organs of an aborted fetus,⁵⁴ and from newborns with conjunctivitis.⁵⁸ Vaginal or cervical colonization with *M. hominis* also has been implicated as a cause of prematurity,⁵⁹ and higher isolation rates have been found in women in whom fever develops after delivery⁶⁰ as well as in women with septic as opposed to afebrile spontaneous abortion. In the last comparison, the proportion of serological response to *M. hominis* was also higher in febrile patients. Of the 51 patients with abortal sepsis in this series, six were shown to have septicemia which, in four cases, was due to *M. hominis*.⁶¹ Since none of these four patients was treated with an effective antibiotic (lincomycin or tetracycline are the most active⁶²) and all recovered, a strong case cannot be made for routine use of antimycoplasmal antibiotics in these cases. In most of the above situations, evidence supports the role of *M. hominis* as an opportunistic pathogen, invading when local tissue trauma has produced a conducive environment.

M. hominis has also been shown experimentally to cause exudative pharyngitis in antibody-free human volunteers,⁶³ but the organism has been isolated from clinical respiratory tract disease so infrequently that it probably should not be considered a respiratory pathogen.⁶⁴

Mycoplasmas and Neoplastic Disease

Reports have appeared in the past decade linking mycoplasmas to human leukemia and lymphoma. These studies were initiated to define a viral cause for human leukemia; thus,

when cytopathic effects were seen and passed in tissue culture, the bodies discovered by electron microscopy were assumed to be viruses. By 1963, the first of these agents identified as a mycoplasma (specifically *M. pulmonis*) had been described. More than likely, it represented a tissue culture contaminant. Subsequently, *M. orale* 1, *M. fermentans*, *M. laidlawii* and *M. hominis* all have been isolated from tissue culture inoculations of leukemic bone marrow. More recently, *M. orale* 1 and *M. fermentans* have also been isolated in artificial medium from bone marrow of leukemics,^{65,66} but these isolations have been sporadic and from only a small percentage of patients studied. Murphy et al⁶⁷ concluded that these isolations represent the invasion of mucous membranes by the normal mycoplasma flora in an immunologically compromised host.

Mycoplasmas and Arthritis

Since Sabin's description of polyarthritis in mice due to a mycoplasma,⁶⁸ at least 12 other mycoplasma species have been shown to cause arthritis in various mammalian hosts under both natural and experimental circumstances.⁶⁹ This has stimulated many studies of the etiologic role of mycoplasmas in human rheumatoid arthritis (RA). A variety of organisms have been recovered in tissue culture inoculation of joint specimens, but for the reasons noted above these isolations are all suspect. Williams, using only an artificial growth medium, noted a significant rate of isolation of *M. fermentans* from synovial fluid of patients with RA.⁷⁰ Subsequently Williams and his associates demonstrated delayed hypersensitivity to an *M. fermentans* antigen in 29 of 43 RA patients.⁷¹ These findings, as yet unconfirmed by other investigators, have renewed interest in the search for an infectious etiologic factor in human RA.

APPENDIX

The common human mycoplasmas are grown easily in a simple medium and can be differentiated tentatively by four chemical tests: glucose oxidation, arginine deamination, urea hydrolysis and methylene blue reduction or growth inhibition (Table 1). Final identification is based upon immunological methods, of which the

TABLE 1.—*Differentiation of Mycoplasmas*

	Methylene Blue Reduction	Glucose	Arginine	Urea
<i>M. pneumoniae</i>	+	+	—	—
<i>M. hominis</i>	No growth	—	+	—
<i>M. fermentans</i>	±	+	±	—
<i>M. orale</i> 1, 2, 3	No growth	—	—	—
<i>M. salivarium</i>	No growth	—	—	—
T-strains	No growth	—	—	+

simplest is the growth inhibition technique of Clyde.*⁷²

The basic growth medium is prepared as follows:

Mycoplasma broth base (Difco or BBL, Inc., or other)	70%
Yeast extract (Micro- biological Associates or other)	10%
Sterilize, then add:	
Phenol red	0.02%
Horse, human, swine or calf serum	20%
Penicillin G	1,000 units per ml
Polymyxin B	25 ug per ml**

From this basic medium three variations are made:

- #1 add 1% glucose and 0.002% w/v methylene blue chloride; adjust pH to 7.6.
- #2 add 0.5% w/v arginine; adjust pH to 6.7.
- #3 add 0.5% w/v urea; adjust pH to 6.0.

The three media are dispensed in aliquots of 5 ml and frozen until needed. They should remain stable for several months.

Throat swabs for *M. pneumoniae* isolation are inoculated only into the methylene-blue glucose media. As methylene blue will inhibit the other oral mycoplasmas,⁷⁵ a color change from violet to yellow or yellow-green between eight and 28 days indicates glucose oxidation and reduction of methylene blue, which presumptively identifies *M. pneumoniae*.

Urine and blood (1 ml) and urethral, vaginal or other swabs from a genitourinary source should be inoculated into all three media (meth-

ylene-blue glucose last). Color change in arginine broth (from orange to red) between 24 and 96 hours suggests growth of *M. hominis*; color change in urea broth (from yellow-orange to red) between 18 and 48 hours suggests growth of a T-strain; after 48 hours, a color change in urea broth could be due to *M. hominis*. Thus, the urea and arginine media must be compared if the urea broth becomes positive after 48 hours. Last, a color change from violet to yellow-green in the methylene-blue glucose medium between five and eight days would suggest the presence of *M. fermentans*.

Any positive culture must be subcultured to bacteriological media without antibiotics to rule out a bacterial contaminant as the cause of the color change.

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*Antiserum for this test are commercially available from several sources.

**Thallium acetate has been omitted from this basic medium because at concentrations required to inhibit Gram-negative bacteria, T-Strain mycoplasmas will also be inhibited.⁷³ This is unlikely with the use of Polymyxin B at this relatively low concentration.⁷⁴

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Surgical Treatment of Atherosclerotic Lesions of the Subclavian Artery

LAWRENCE H. COHN, M.D., *Boston*, THOMAS J. FOGARTY, M.D.,
PAT O. DAILY, M.D., JAMES F. SILVERMAN, M.D., AND
NORMAN E. SHUMWAY, M.D., *Stanford*

■ *Of eight patients with atherosclerotic lesions (seven occlusive, one aneurysmal) of the subclavian artery, five were operated upon because of the subclavian steal and three for severe ischemia of the hand and fingers.*

Removal or bypass of these lesions was uniformly successful in relieving symptoms. In most cases transcervical carotid-subclavian saphenous vein bypass graft is the treatment of choice, provided no carotid obstruction exists or, if there is obstruction, it can be dealt with at operation.

ARTERIOSCLEROTIC LESIONS of the subclavian artery, though considerably less common than carotid or lower extremity lesions, may produce ischemic syndromes involving the cerebral and upper extremity circulation. This report details the clinical course, the distinctive ischemic syndromes, and results of surgical therapy in patients operated upon for subclavian arterial lesions.

Clinical Material

In the period from 1968 to 1970, eight patients with atherosclerotic lesions of the subclavian artery were operated upon at Stanford Medical Center. Clinical data are summarized in Table 1. There were six women and two men. The age range was 32 to 73 years, the average 55 years. Five patients had symptoms and radiographic signs related to the cerebral circulation, the so-

called "subclavian steal." The symptoms most frequently noted were ipsilateral ataxia, vertigo, syncope, decreased vision of the left eye, and transient ipsilateral weakness of the arm—symptoms referable to ischemia of the hindbrain. Three patients had symptoms and signs referable to severe ischemia of the ipsilateral upper extremity. Of these three patients, two had obstructive lesions (Cases 1 and 6), and one had an aneurysm with emboli to the fingers (Case 4). All patients underwent arch aortogram and angiography of the cerebral circulation. In only one of the eight patients were significant obstructive lesions of the other main extracranial cerebral vessels found; five lesions were found in the left subclavian and three in the right.

Surgical Treatment

Four patients underwent endarterectomy (three transthoracic, one transcervical), one aorto-subclavian bypass, one had resection and grafting of the proximal left subclavian for aneurysm, and two had transcervical bypass, one to the distal brachial and one to the subclavian artery

From the Division of Cardiovascular Surgery and the Department of Radiology, Stanford University School of Medicine, Stanford.

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Dr. Cohn's present address is Division of Cardiovascular Surgery, Peter Bent Brigham Hospital, Boston 02181.

Reprint requests to: N. E. Shumway, M.D., Department of Surgery, Division of Cardiovascular Surgery, Stanford University School of Medicine, Stanford, Ca. 94305.

TABLE 1.—Data on Eight Cases of Subclavian Reconstruction

Case No.	Sex	Age	Symptoms	Physical Exam	X-ray Study	Operation	Result
1.	M	66	Vertigo, blackout spells	110 syst. L. arm 140 syst. R. arm ↓ vision L. eye	Subclavian steal on L. 90% stenosis L. subclav.	Transthoracic L. subclavian TEA	No further spells 4+ L. radial pulse 36 mo. follow-up
2.	F	62	"Subclav. steal" vertigo, severe hypercholesterolemia	50 mm difference, R & L arm B.P. 1+R, 2+L radial	R. subclav. obst. total; distal fills from R. vertebral; narrowed L. subclav.	R. transcervical subclav. TEA	4+ radial pulse R. arm. B.P. > than L. 24 mo. follow-up
3.	M	52	Weakness R. arm, vertigo to right	R. arm B.P. 90 syst. L. arm 170	R. subclav. steal stenosis L. vertebral	Ao-R subclav. bypass with 10 mm dacron graft	B.P. 160 R. & L.; no R. arm claudication; 20 m. follow-up
4.	F	32	Intermittent ischemia fingertips	L. supraclavicular mass	Saccular L. subclavian aneurysm	L. vertebral ligated, aneurysm replaced with 8mm dacron graft	4+ L. radial; B.P. 120/86, 12 mo. follow-up
5.	F	55	Syncope	1+ R. radial pulse	Localized obst. R. subclav. at innom. takeoff	R. subclav. TEA	No syncope, 4+ right radial pulse, 9 mo. follow-up
6.	F	73	Tender fingers L. hand	Gangrene L. index finger, ischemia L.	90% L. subclav. stenosis, 90% stenosis L. vertebral, ulcerated lesion, L. carotid	L. carotid TEA, L. carotid-subclavian bypass	Gangrenous changes gone in 5 days, warm hand, good pulse, 6 mo. follow-up
7.	F	37	↓ vision L. eye, vertigo with exercise L. arm, lupus	1+ L. radial pulse, ↓ B.P. L. arm	90% stenosis takeoff L. subclavian, subclavian steal	Transthoracic L. subclavian TEA	Asymptomatic, 6 months follow-up
8.	F	63	Severe right hand claudication	No pulse R. arm	Long stenosis R. subclavian	R. carotid-brachial bypass	Complete return of function R. arm, 6 months follow-up

R=right; L=left; BP=blood pressure; TEA=thrombo-endarterectomy

utilizing autogenous saphenous vein. One patient undergoing carotid-subclavian bypass also had a concomitant carotid bifurcation endarterectomy because of an ulcerated, atheromatous lesion. In both patients with carotid saphenous vein bypass operative arteriograms were made to insure technical adequacy.

The eight patients were followed for periods of six to thirty-six months.

Results

There were no operative deaths or major post-operative complications. Patients who were operated upon for hand and digital ischemia or arm claudication or both, had complete relief within a week after operation and there was no recurrence. Blood pressure in these extremities has returned to normal, function of the hand has returned, and gangrene of the fingertips noted in Case 6 was completely reversed.

Patients with symptoms of cerebral ischemia were also relieved in all cases; there were no further syncopal attacks, vertigo, or intermittent paresis, and improvement in vision in the ipsilateral eye was noted in both patients who said it was a major symptom. Radial pulses returned in all these patients and blood pressure returned toward the level of the opposite arm in all cases. There has been no return of symptoms during the follow-up period.

Illustrative Case Reports

Individual case reports illustrate some important clinical and therapeutic points.

Case 8 (Table 1). A 63-year-old woman noted increasing inability to use her right hand in performing household chores. She could not write her name without stopping to rest, nor could she wash her dishes without stopping several times. She also complained of similar but less

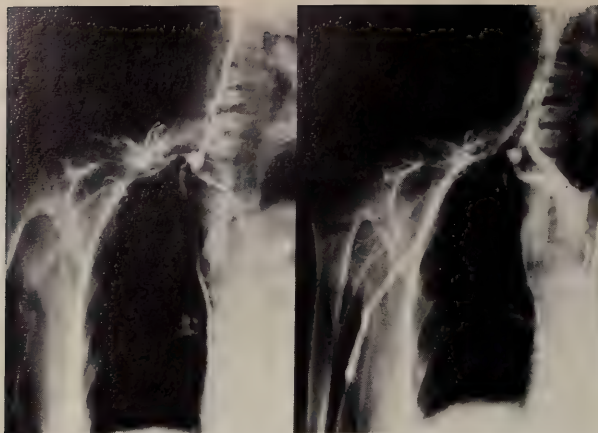


Figure 1.—Selective innominate arteriogram before and after right carotid-brachial saphenous vein bypass in Case 8 (Table 1). The subclavian artery on the left is also diffusely narrowed; the right brachial artery can be seen to fill faintly in the distal arm. Postoperatively, on the right, the saphenous vein graft fills after injection into the common carotid artery.

severe symptoms in her left hand. Her right hand was pale and cool, and there was no radial pulse; a 1+ radial pulse was felt in the left hand, and blood pressure in the left arm was 100/60 mm of mercury. An arch aortogram (Figure 1) revealed diffuse narrowing of the first and second parts of the right subclavian artery as well as the axillary and proximal brachial artery. A right retrograde brachial arteriogram clearly demonstrated patent distal brachial circulation.

After ascertaining that the right common carotid bifurcation was free of atherosclerotic obstruction, a saphenous vein common carotid distal brachial bypass graft was performed under general anesthesia and systemic heparinization. An internal shunt was used during the carotid anastomosis, which was made end-to-side with running 6-0 Tevdek® suture. The graft was tunneled subcutaneously across the clavicle to the distal one-third of the upper arm, where the brachial artery had been exposed. The graft was then sutured end-to-side with running 6-0 Tevdek to a normal brachial artery.

A postoperative arteriogram showed the vein graft patent (Figure 1). Postoperatively, the blood pressure was 140/80 mm in the right arm, the color improved substantially, and within ten days the patient was able to do all her housework without difficulty. After the operation there were no cerebral insufficiency, visual or vertiginous symptoms.

Case 6 (Table 1). A 73-year-old woman presented with early gangrene of the left index finger and severe ischemia of all her left fingertips of about two weeks' duration. She had been a heavy smoker but had stopped two months before admission. She denied any traumatic accident. She had no pulses or blood pressure in the left arm and her index finger was cold, blue-black and extremely tender.

An arch aortogram and cerebral angiography showed 90 percent stenosis of the origin of the left subclavian and of the origin of the left vertebral arteries (Figure 2, *left*). There was a suggestion of an ulcerated lesion of the left internal carotid artery at the left carotid bifurcation by selective angiograms (Figure 2, *center*). Palpation of the left carotid bifurcation confirmed a significant atheroma consistent with the radiologic lesion.

Left carotid bifurcation endarterectomy and saphenous vein carotid-subclavian bypass in the neck were performed under general anesthesia and systemic heparinization. During the carotid occlusion, an internal shunt was used.

Postoperative angiography indicated a satisfactory technical result (Figure 2, *right*). By the end of the first postoperative week, the gangrenous changes had completely resolved and the patient had pulses and equal blood pressure in the arm. She had no postoperative neurologic sequelae.

Comment: It is postulated that obstruction of the ipsilateral vertebral artery precluded any "subclavian steal" and any increase in collateral flow to prevent ischemia of the fingers.

Case 7 (Table 1). A 37-year-old housewife with discoid lupus complained of vertigo with exercise of her left arm, occasional diplopia, and a general decrease in the vision of her left eye during the six months before admission. There was a 1+ pulse in the left arm and lower blood pressure in that arm than in the right.

An arch aortogram and cerebral angiograms showed 90 percent stenosis of the left subclavian artery at its origin (Figure 3). There was radiographic evidence of subclavian steal since retrograde left vertebral filling could be seen in late films of the angiogram series. There was no other abnormality of the cerebral or extracranial circulation.

Because of her age and the possibility of arteritis secondary to the lupus, left thoracotomy

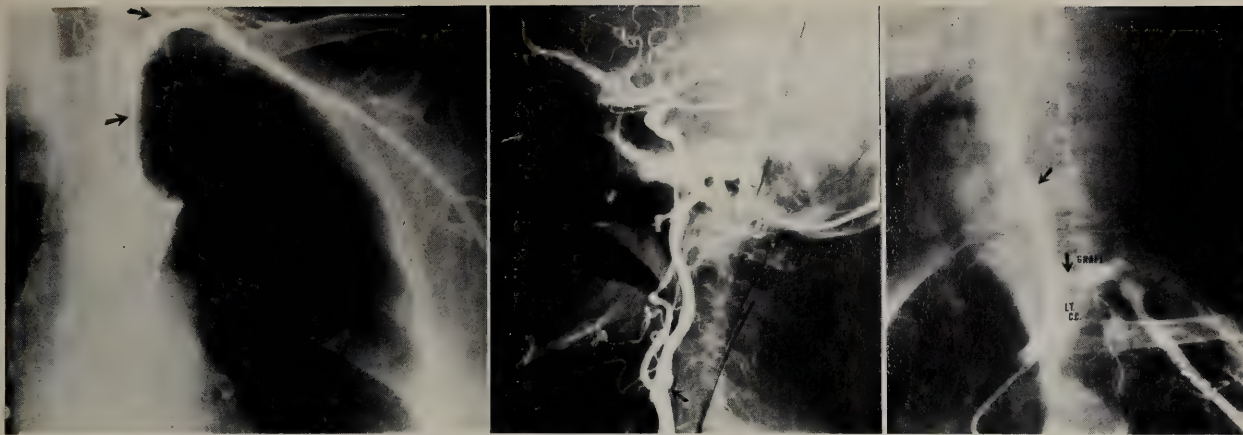


Figure 2.—*Left*, selective left subclavian arteriogram in Case 6. Arrows point to the 90 percent stenosis of the proximal subclavian and the takeoff of the left vertebral. *Center*, selective left carotid injection demonstrating an ulcerated atheroma in the left internal carotid. *Right*, postoperative selective angiogram of the left common carotid artery (LT. C.C.). The three arrows point to the origin, course and termination of the carotid to left subclavian (LT. S.C.) venous bypass graft.

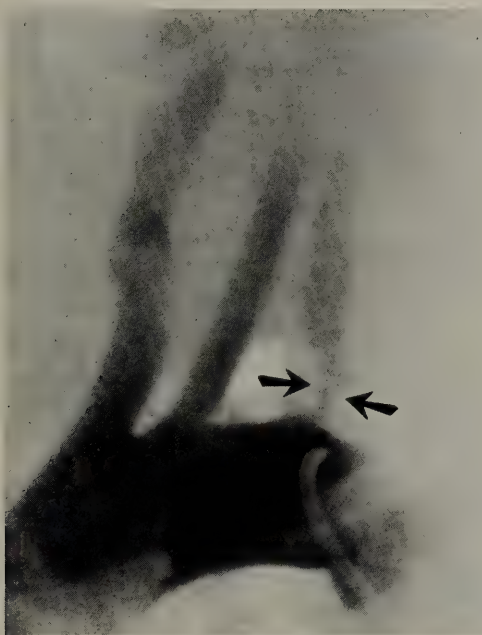


Figure 3.—Aortic arch angiogram in Case 7, illustrating 90 percent stenosis of proximal left subclavian artery.

and left subclavian endarterectomy were performed. A thick atheromatous core extending into the aortic arch was removed through a longitudinal incision in the proximal left subclavian artery. The arteriotomy was repaired with running 5-0 Tevdek. There was no evidence of arteritis either grossly or by microscopic sections. The patient made uneventful recovery, pulses and normal blood pressure were restored in the left arm, and she noted immediate im-

provement in the vision of her left eye. In seven months of follow-up she had no recurrence of vertigo or diplopia.

Comment: An unusual case because of atheromatous disease at age 37 and the presence of severe cerebral symptoms with a solitary subclavian lesion without carotid obstruction.

Discussion

The cases summarized here serve to point out the distinctive, easily reversible syndromes associated with atherosclerotic lesions of the subclavian artery. Ischemia of the hand and forearm in the absence of ischemia of the hindbrain may vary a great deal in severity and the symptoms often pose a problem to the clinician as to when to investigate and treat. Our policy has been to recommend diagnostic workup and surgical therapy if the patient is a reasonable risk in other respects, and if the ischemic symptoms of the forearm and hand are severe enough to interfere with normal activity, as in Case 8. Clearly, the other end of the spectrum, as illustrated in Case 6, offers no problem in management and workup, and operative therapy should be carried out as soon as possible. If significant, discrete stenosis is demonstrated by angiograms, we believe the direct surgical approach by the carotid-subclavian bypass operation or endarterectomy is preferable to cervical sympathectomy.

The problem of the ischemic hindbrain in conjunction with a discrete proximal subclavian

lesion is somewhat more nebulous. The so-called "subclavian steal," a siphoning of blood from the circle of Willis down the ipsilateral vertebral, is usually associated with a decrease in peripheral resistance distal to the subclavian arterial stenosis, that is, in the exercising muscle of the forearm. The syndrome was named by Fisher¹ in an editorial commenting on two cases studied by Reivich et al in 1961.² Contorni³ first described this syndrome in the modern literature but according to Fields,⁴ it was Smyth who, in 1864, made the first reference to the possibility of retrograde flow via the vertebral into the distal subclavian beyond a more proximal occlusion. Certain interesting observations about this syndrome have recently been made by Ehrenfeld, Chapman and Wylie.⁵ In the great majority of their cases the subclavian steal is either asymptomatic or associated with internal carotid artery obstruction, and when the carotid obstruction is cleared, despite the persistence of the subclavian steal radiographically, the patients usually become asymptomatic; only 33 of 125 patients (26 percent) had isolated subclavian steal with symptoms severe enough to require operation.⁵

The exact reason why patients with otherwise normal cerebral and carotid circulation have the clinical effects of subclavian steal with an isolated subclavian stenosis must lie in peculiarities of the circle of Willis. Eklof and Schwartz,⁶ in an elegant canine experiment, showed that cerebral blood flow, electroencephalogram or cortical oxygen tension was not changed with the subclavian steal, even with vasodilatation of the ipsilateral forelimb. These findings emphasized the autoregulatory capabilities of the cerebral circulation, a phenomenon that probably accounts for the clinical observation that it is unusual for the subclavian steal *per se* to result in cortical cerebral ischemia. This observation correlates with the clinical observations of Ehrenfeld et al.⁵ Three patients in our series had a solitary subclavian lesion without other obvious cerebral obstructions. More careful radiologic delineation of the entire circle of Willis may demonstrate abnormalities of the posterior communicating vessels in these and future patients to explain the clinical findings. Indeed, Lord, Adar and Stein⁷ showed evidence of disconnection of the circle of Willis between the territories of the carotid and vertebral arteries in a significantly higher proportion of patients

with vertebrobasilar insufficiency and the subclavian steal syndrome.

Operation for lesions of the subclavian artery has undergone a gradual evolution from procedures necessitating thoracotomy to those requiring cervical bypass.⁸ Crawford et al⁹ reported that the mortality with thoracic procedures (thrombo-endarterectomy or aorto-subclavian bypass) during the first years of their series was 20 percent; with extrathoracic procedures for similar lesions, the mortality has fallen to less than 3 percent. Similarly, Ehrenfeld, Chapman and Wylie⁵ noted a 9 percent mortality after the transthoracic approach in 14 patients.

Other than for diagnostic indications (Case 7), or in conjunction with an additional intrathoracic cardiovascular procedure, our current treatment of choice is the transcervical saphenous vein bypass grafting from the common carotid distal to the subclavian obstruction. The ipsilateral carotid bifurcation thrombo-endarterectomy (TEA) is performed, if indicated, as in Case 6. Controversy has existed as to the "steal" effect on the cerebral circulation from carotid-subclavian bypass,¹⁰ but both extensive clinical experience^{5,8,9} and experimental studies¹¹ have clearly shown that a vascular steal does not occur after carotid-subclavian bypass provided the carotid circulation is unobstructed. Flowmeter studies¹¹ have further demonstrated that flow in the common carotid trunk increases to accommodate the additional circulation to the left subclavian artery.

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Sciatic Injection Neuropathy

BARTON A. BROWN, M.D., *San Francisco*

■ *Prevention of sciatic injection neuropathy can best be accomplished by teaching that the injection should be made into the gluteal mass in the upper outer quadrant rather than the buttock, and that the needle should be introduced in a plane perpendicular to the surface of the bed when the patient is lying prone. Failing prevention, one must strive for early and correct diagnosis, especially in infants, and carry out exploration with internal and external neurolysis if there is no evidence of improvement within two to three months.*

THE PROBLEM OF SCIATIC nerve injury secondary to gluteal injection is a persistent one despite widespread teaching that the upper outer quadrant should be the site for injection, or that other sites should be used in children. It is difficult to restore a damaged nerve to normal function and the difficulty is compounded by the almost invariable medico-legal accompaniments.

Thus, the problem is two-fold—the education of personnel to avoid causing injection neuropathy, and prompt recognition, diagnosis and treatment if it does occur.

The typical sciatic injection neuropathy consists of severe involvement of the anterior compartment of the leg (anterior tibial, peronei, toe extensor muscles), usually with complete foot drop. There is usually weakness in the gastrocnemius muscle, although less pronounced than in the anterior compartment. Less frequently, there may be involvement of the hamstrings. The ankle jerk is usually absent and there is a variable sensory loss over the dorsum of the foot and lateral calf.

It is said that in 75 percent of cases there is immediate nerve damage without pain,¹ in 16 percent immediate nerve damage with pain in a

sciatic distribution, and in nine percent delayed paralysis without pain. These data are difficult to interpret because in most of the reports the patients were infants and pain therefore difficult to assess.

The question to answer is why do injection neuropathies continue to occur despite widespread teaching that the upper outer quadrant is the place for injection. It appears that most medical personnel responsible for gluteal injections believe that the safe site is the upper outer quadrant of the *buttock*, when indeed it is the upper outer quadrant of the *gluteal mass*,¹ a considerably larger target since it originates at the anterior superior iliac spine. In addition there is widespread impression that the needle angle should be vertical to the skin surface through which it is pushed, but Johnson and Raptau² showed in autopsy studies on infants that this will frequently result in injection of material into or near the sciatic nerve. They pointed out that if the needle is introduced in a plane vertical to the surface of the bed with the patient in the prone position, the nerve can almost invariably be avoided.

Besides needle length and direction, variation in thickness of the gluteal fat pad (from 1 to 9 cm, depending upon the age and state of nutri-

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Reprint requests to: B. A. Brown, M.D., 2001 Union Street, San Francisco, Ca. 94123.

tion of the patient) must be taken into account; for unless the fat is penetrated and the muscle reached, the purpose of the injection is defeated.

The clinical picture evolves because the needle usually approaches the nerve from the lateral aspect and the peroneal portion of the sciatic nerve is the more laterally placed of the two major divisions. In addition, the peroneal division is somewhat more superficial, and in 15 percent of cases,³ it pierces the piriformis or leaves the pelvis above that muscle and thus is more vulnerable than the tibial component.

Virtually every injectable substance has been implicated in sciatic injection neuropathy, but the most frequent offenders are antibiotics, probably because they are used oftener and the buttock is usually the site chosen for injecting them. Whether injecting a material in the region of the sciatic nerve but not actually into the nerve can cause neuropathy is undecided. The separate investigations of Tarlov⁴ and Hochstetter^{5,6} in animals indicate that the offending material must be deposited within the nerve sheath to cause neuropathy.

The diagnosis of sciatic injection palsy is not always simple. Because it occurs more often in infants, the observation of foot drop may be considerably delayed. In addition, many patients receiving gluteal injections are quite sick and discovery may be delayed until they are convalescing. The following cases will illustrate some of the difficulties encountered. Once the diagnosis is confirmed, proper treatment can be instituted. During six to eight weeks of observation before neurosurgical intervention is undertaken, physical therapy should be given and a foot-drop brace provided. Consideration of stabilizing procedures or posterior tibial tendon transfers should be delayed until no hope remains for neurologic recovery. Should improvement begin, only further supportive measures are indicated.

Case 1. The patient, a 6-year-old girl, was given an injection in the left gluteal area for relief of pain after tonsillectomy. She had immediate local pain, and the following day weakness was noted with numbness in the left foot. She had considerable pain at night and was found to have weakness in the gluteal muscles, the hamstrings and in the anterior and posterior leg muscles. She had numbness on the dorsal foot and lateral calf. The left ankle jerk was absent.

On examination three weeks after the injection definite improvement was noted and in three months recovery was complete.

This case is an example of spontaneous improvement; only physical therapy was needed to assist in recovery. However, if the patient does not improve in six to eight weeks as judged by either electromyographic or clinical testing, then neurolysis should be carried out. This should include exposure of the sciatic nerve through a question mark-shaped incision with reflection of the gluteus maximus medially. Both internal and external neurolysis must be performed, and intra-operative electrical stimulation before and after the neurolysis, both proximal and distal to the lesion, is helpful in determining prognosis.

Case 2. A 9-year-old boy had an electrical sensation immediately after a penicillin injection in the left buttock. Numbness and weakness also were noted immediately. Treatment was expectant. Four months after the injection, there was complete foot drop and weakness of plantar flexion of the foot as well. Ankle jerk was diminished and the calf was atrophic. There was numbness in the anterolateral calf and dorsal foot. Internal neurolysis was carried out with the aid of magnification, to relieve the dense intraneural scarring. Slow recovery ensued. A year and a half after operation the patient had discarded his foot-drop brace and was engaging in all of his normal activities despite residual weakness in his toe extensors.

Case 3. A 3-year-old girl received an injection of penicillin and hydroxyzine hydrochloride (Vistaril®) in the right gluteal area before tonsillectomy. After the operation, right foot drop was noted. On subsequent examination the circumference of the right calf was 3 cm less than the left, and there was complete paralysis of the anterior leg muscles and moderate to pronounced weakness of the gastrocnemius group and the toe flexors. Hyperesthesia was noted in the dorsum of the foot. The right ankle jerk was absent. Four months after the injury there was no improvement and electromyography showed fibrillations in both the anterior and posterior leg muscles without involvement of the hamstrings or gluteal muscles. Sciatic internal neurolysis was carried out. The lesion was at the level of the sciatic notch, as is usually the case. There was pronounced internal scarring of the nerve, more pronounced in the peroneal than in the tib-

ial portion. Despite the poor condition of the nerve, there was some intraoperative improvement to electrical stimulation after neurolysis. Two days later the patient could move the extensors of her foot and subsequently she had complete recovery. Eight months after operation the only discernible changes were a 3 mm decrease in the size of the right calf, and the operative scar.

Case 4. A 21-year-old woman took an overdose of sleeping pills and was found unconscious by her friends who tried to awaken her by a gluteal injection of "speed." Soon afterward she was aware of numbness and weakness in the left lower extremity. On examination four months after the injection, mild weakness of the hamstrings, pronounced weakness of the gastrocnemius and soleus, and slight weakness in the anterior leg muscles were noted. There was atrophy of the calf. Sensation in the sole and lateral foot was decreased and the Achilles reflex was absent. Internal neurolysis of severe scarring in the tibial division of the sciatic nerve was carried out. Within ten days there was improvement in plantar flexion. A year and a half later muscle strength was normal but there was still diminished sensation on the ball of the foot and absence of ankle jerk. The patient was able to use the left lower extremity in normal fashion, however.

Case 5. A 50-year-old man received an intragluteal injection of penicillin for a cold. He had immediate pain in the buttock and two days later, when he got up from bed, noted pain extending into the right lower extremity. The pain increased on activity and was relieved by rest. There was tenderness in the sciatic notch, and the right ankle jerk was absent. The attending physician made a diagnosis of injection neuropathy, as did several who examined the patient subsequently. Ultimately, a sciatic nerve exploration was carried out and no abnormality of the nerve was observed. A myelogram showed significant defects at the fourth and fifth lumbar disc levels on the symptomatic side. Questioning elicited a history of previous disc operation on the left and two previous episodes of sciatica on the right.

Discussion

Our experience, as illustrated by cases herein reported, indicates that surgical intervention can improve the prognosis of sciatic injection palsy. Review of the literature also supports a role for surgical intervention. Arrest of growth of the foot occurs in about half of infants with sciatic palsy; a "satisfactory improvement" is achieved in only about one-third⁷ of untreated cases. Many patients require a foot brace permanently. More, the longer surgical intervention is put off, the greater the likelihood of permanent changes in muscles, joints and skin. Such changes will not be reversed by good surgical treatment if it is too long delayed.

Unquestionably, the diagnosis of injection palsy in Case 5 was incorrect. The patient had a protruded lumbar disc with root compression. The early diagnostic errors resulted in litigation and pecuniary award, however, even though the diagnosis was not supported by the findings, the history, or the studies. When the sciatic nerve is injected, any pain that occurs is usually immediate and throughout the lower extremity. It is not related to activity, and indeed is frequently worse at night. In such cases weakness and sensory loss are usually most severe in the peroneal distribution. Electromyography is frequently helpful in corroborating the diagnosis.

TRADE AND GENERIC NAMES OF DRUGS

Vistaril®hydroxysine hydrochloride

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The Pajaroello Tick Bite

The Frightening Folklore and the Mild Disease

ROBERT M. FAILING, M.D., C. BENTLEY LYON, B.S., (*Forestry*),
AND JAMES E. MCKITTRICK, M.D., *Santa Barbara*

■ *The pajaroella tick (Ornithodoros coriaceus) has a fairly wide distribution in the coastal and mountainous areas of California and Mexico. Persons engaged in outdoor activities there, are frequently bitten. Little is written in the medical literature concerning the tick and its bite. What has been written is liberally injected with frightening folklore that sometimes results in overzealous treatment. Conservative and supportive therapy is advisable and only rarely should one have to resort to such treatment as excision of an area of tissue necrosis to prevent ulceration and prolongation of healing.*

"ITS BITE MORE FEARED than that of the rattlesnake"^{1,2} appears all too often in the meager literature generally available to the practicing physician about the common California arthropod *Ornithodoros coriaceus*, called pajaroello.

In reviewing the medical literature two things become immediately apparent. First, little has been written and, second, that which has is of questionable accuracy. Even as recent a publication as that of the Communicable Disease Center—"Ticks of Public Health Importance and Their Control"² propagates the "more feared than the rattlesnake" myth.

The most accurate data are found scattered through various communiques, memoranda and

bulletins of the U.S. Forest Service, the California State Agricultural Department, and certain entomological publications, all of which are generally beyond the immediate reach of physicians.

The purpose of this paper, therefore, is one of information on the pajaroello and its bite.

History

Pajaroello (pronounced pa har wayo) comes from the Spanish "paja," meaning straw, and "huello," the undersurface of a hoof. It is also called Pajahuello, leatherback or greyback tick, and, in Mexico, "Talaja."

This arthropod is found in California and Mexico in an area extending from Humboldt County on the north to the Mexican isthmus of

From the Department of Pathology, Santa Barbara Cottage Hospital.
Submitted July 12, 1971.

Reprint requests to: R.M. Failing, M.D., Department of Pathology,
Santa Barbara Cottage Hospital, Post Office Box 689, Santa Barbara,
Ca. 93102.



Figure 1.—Dorsal and ventral surfaces of unfed *Ornithodoros coriaceus* (pajaroello tick).

Tehuantepec and the state of Chiapas on the south. With the exception of an obscure report from Paraguay in 1888, it has never been reported outside of this area. The pajaroello tick was first described by Koch in 1844 from specimens taken in Mexico. Nuttall and his coworkers,³ the first to report its presence in California (in 1904), described specimens collected near Los Olivos in Santa Barbara County.

Its habitat extends from the coastal mountains of California eastward to the Sierra foothills and the Tehachapis, ranging from sea level to over 7500 feet elevation.⁴ It is most prevalent in the dry, hot mountainous areas of Monterey, San Luis Obispo, Santa Barbara, Kern, Ventura and Los Angeles Counties, and it has been found in more than half of California's 58 counties.⁵

The tick abounds in deer beds among low scrub oaks (*Quercus dumosa*). Its favorite hosts are the mule deer (*Odocoileus* species) and range cattle.

Life Cycle and Feeding Habits

The life cycle involves four stages: egg, larva (6-legged), nymph and adult (both 8-legged). The larvae, nymphs and adults can go without a blood meal for as long as two years. Nymphs and adults feed rather rapidly, taking a blood meal in from a half hour to an hour and a half. Larval forms, however, feed on their host for a number of days.^{6,7}

Loomis and Furman⁶ expressed belief that rapid truck transportation of cattle (infested by long-feeding larvae) from one grazing area to

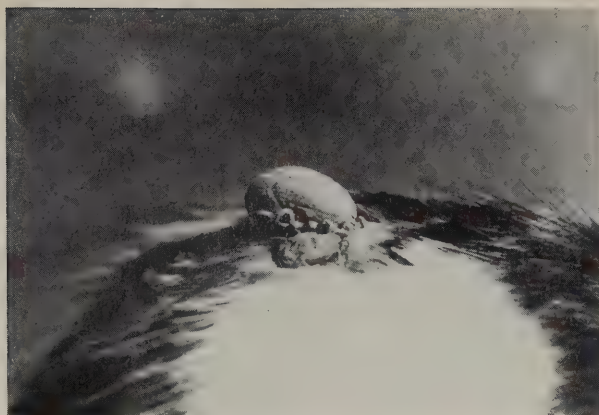


Figure 2.—Two pajaroellos on back of laboratory animal (rat). The larger has been taking a blood meal for 30 minutes; the smaller (unfed) has been positioned for comparison.

another may be an important factor in extending the geographic distribution of the tick.

The pajaroello differs from other ticks in that it does not attach to moving hosts but lies in wait for animal or man, crawling to its host, biting, feeding, and then dropping back to the ground. It is up to one-half inch long and very difficult to see even to the experienced observer because of its similarity in color and size to bits of soil (Figure 1). The blood meal of an adult lasts about 30 minutes and can increase its weight sixfold (Figure 2).

The Bite, Folklore and a Case Report

The bite was first described as "intolerably sharp and painful . . . with intermittent irritation that persisted after four months."⁸ Herms⁸ reported in some detail the "disagreeable feeling . . . irritability and numbness" of a lesion lasting for several weeks and still evident at three months. Local folklore in one area reports that "three bites will result in certain death."⁹

The lay press stimulates the public's imagination in reporting ". . . most dangerous to man is the dreaded pajaroello . . . It is one of two venomous ticks in the West. The venom is similar to that of a rattlesnake . . ."¹⁰

Case Report. In May 1970 six healthy men from 40 to 57 years of age camped at 2,000 feet elevation under a stand of scrub oak on the banks of the Sisquoc River in the San Rafael Wilderness area of the Los Padres National Forest, Santa Barbara County. Four of the six, including two of the authors, (RMF and CBL) received



Figure 3.—Pajaroello bite approximately 12 hours old on left lateral thigh of author (RMF).

This painless lesion had reached maximum size (20 mm in diameter), became mildly indurated, pruritic, did not ulcerate and gradually healed during the next four weeks.

painless bites numbering from two to seven on various parts of the body, including head, face, arms, back, legs, feet and toes. Several ticks identified as *Ornithodoros coriaceus* were easily found within sleeping bags and about the camping area. The bites initially appeared as small macules. Within 12 hours a central papule up to 2 mm surrounded by a zone of erythema with an intense peripheral ring of hyperemia was noted (Figure 3). The lesions varied from 10 to 30 mm in diameter. Some were associated with mild to moderate edema. None were painful and only minimal itching was noted.

During the next two weeks the lesions decreased in size to macules 3 to 4 mm in diameter with mild to moderate induration but no ulceration. These, in turn, gradually subsided and by four weeks there was little or no visible reaction. One of the four men bitten underwent extensive laboratory investigation, including hematologic, SMA-12/60 chemistry studies and febrile agglutinins (including typhoid O,H,Para A, Para B, Brucella, OX-19, OX-K and tularemia). In addition, acute and convalescent serum studies were done by the California Viral and Rickettsial Disease Laboratory. No abnormal findings were recorded during six weeks of such studies.

The indurated areas about two of the bites were excised at 72 hours. Microscopic changes were nonspecific, showing a central focus of acute necrosis, edema and congestion with a mild cellular infiltrate about dermal capillaries.

The latter was composed of round cells with a few polymorphonuclear leukocytes. Fibrin thrombi and fibrinoid necrosis were not present. The lesions were most consistent with a nonspecific allergic vasculitis.

Severe Reactions to Bite

Severe systemic reactions have been reported but fortunately they are very rare. Probably they are related to previous bites with sensitization to some substance in saliva secretions. Such reactions are rather rapid in onset, with edema, erythema and pain. Tissue necrosis, ulceration and a prolonged period of healing follow. No doubt the previously mentioned early reports^{3,8} concerned persons who had been sensitized by previous bites.

Most bites occur in persons engaged in outdoor, back country activities, such as Forest Service personnel, campers, hunters, fishermen, utility company workers, survey crews and ranchers. Large numbers may be bitten at one time, as in the case of fire fighting crews seeking rest or sleep in shaded areas frequented by deer and cattle where the tick may abound.

Treatment

In general, treatment reported has been aggressive. Loomis and Furman⁶ pointed out that the treatment in some cases may be worse than the bite. In many cases incision and suction, as with snakebite, has been used.

It would appear that conservative treatment is in order—cleansing of the wound, local compresses and administration of tetanus toxoid. Only in the event of a rare systemic allergic reaction with severe pain and swelling should one resort to more vigorous therapy. Benadryl and ACTH may be of help.⁵ In cases where tissue necrosis has occurred, consideration should be given to excision and primary closure, as has been done in the treatment of brown (violin) spider bite,¹¹ to prevent the ulceration and prolonged healing that has been reported in some cases. The ulceration and scarring associated with brown spider bite is directly related to injection of a venom, but in the case of the pajaroello it is a local sensitization or Arthus phenomenon with tissue necrosis and ulceration. The tick contains no known toxin or venom.

ACKNOWLEDGEMENT: The authors wish to thank William Hansen, Supervisor (since retired) Los Padres National Forest, for his cooperation in securing the pajaroello specimens from the Sisquoc River area.

We are also indebted to Lawrence J. Pinter, Past Director, Santa Barbara Museum of Natural History, and Franklin Ennik, Assistant Vector Control specialist from the California Department of Public Health for identification of the tick species and other technical data.

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THERAPY FOR URINARY TRACT INFECTION

When do you use long-term continuous therapy in patients with a urinary tract infection?

I find that this is usually not necessary in the individual who comes to the office with the first, second, or third episode. But you will occasionally have an individual . . . who has had ten or fifteen episodes closely spaced so that he cannot really work, live, or function well. In this individual I would use what I call a prophylactic regimen for a period of a month or two, usually using nitrofurantoin to quiet down the whole situation, . . . in a sense to break the cycle. I would restrict it to that particular group. After having previously tried intermittent specific therapy for each episode which usually takes care of 80 to 90 percent of the population, I find this approach impressive—it is effective.

There is one additional time when I would use long-term therapy. . . . I pick out those people who have clear renal involvement whom we know will not respond readily to the usual short course of treatment, people who have a high rate of relapse. These are the people I treat for a year. We feel, though the data are hard to come by, that we have a much higher rate of true cure in these people than has been seen under any other conditions. . . . We use methenamine mandelate (Mandelamine®) most often for this purpose.

—PANEL DISCUSSION ON CHRONIC INFECTIONS OF THE URINARY TRACT

Extracted from *Audio-Digest Internal Medicine*, Vol. 18, No. 10, in the Audio-Digest Foundation's subscription series of tape-recorded programs. For subscription information: 1930 Wilshire Blvd., Suite 700, Los Angeles, Ca. 90057

Importation of Shiga Bacillus Dysentery Into California

Clinical and Public Health Significance

S. BENSON WERNER, M.D., RONALD R. ROBERTO, M.D., AND
JAMES CHIN, M.D., *Berkeley*

■ *Concurrent with the regional epidemic of classic Shiga dysentery in Central America during 1969 and 1970, a pronounced increase in the isolation of Shigella dysenteriae type 1 was noted in California. A retrospective study of 20 cases diagnosed in California in 1969 and 1970 revealed that 18 of the patients had traveled to Central America or Mexico during or immediately before the onset of symptoms. Sixteen were known to have been admitted to hospital; there was one death. Despite the concern that such importations might result in epidemics in this country among groups living in crowded, unsanitary settings, no definite secondary transmission was identified in this study. The problems of differential diagnosis, laboratory isolation of the agent, chemotherapy, and epidemic control are discussed.*

SINCE JANUARY 1969, a particularly virulent form of bacillary dysentery has reemerged in epidemic form and spread from its apparent origin in Guatemala to other areas of Central America and Mexico.¹ This epidemic was caused by the classic Shiga bacillus, *Shigella dysenteriae* type 1. In the United States this is an extremely rare serotype which accounts for only a fraction of 1 percent of all *Shigella* isolates reported to the Center for Disease Control (CDC).¹ The disease is characterized by diarrhea, frequently with blood and mucus, tenesmus, abdominal cramps,

tenderness, fever and toxicity. Deaths are common, especially in children. The bacillus spreads via the fecal-oral route and is disseminated easily where sanitation is primitive. Direct person-to-person as well as water-borne transmission was thought responsible in the spread of this disease in Central America.²

Concurrent with the Central American outbreak in 1969 and 1970, isolations of Shiga's bacillus were reported in California and nationally in greater numbers than ever before. While only three isolations of *S. dysenteriae* type 1 were identified at the Microbial Diseases Laboratory of the California State Department of Public Health between 1964 and 1968, nine isolates were identified in California in 1969 and 11 in

From the Infectious Disease Element, California State Department of Public Health.

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Reprint requests to: S. B. Werner, M.D., Bureau of Communicable Disease Control, California State Department of Public Health, 2151 Berkeley Way, Berkeley, Ca. 94704.

1970. Exclusive of California, 29 isolations of *S. dysenteriae* type 1 were reported nationally to the CDC during the years 1969 and 1970, whereas only five had been reported in the previous four years.³

A retrospective study was made of the 20 California patients diagnosed in 1969 and 1970 to define their sources of exposure and other pertinent epidemiologic features. It is our purpose to describe those findings and comment on laboratory methods, treatment, and control measures.

Materials and Methods

The Microbial Diseases Laboratory of the California State Department of Public Health serves as a reference laboratory in California for the identification of *Shigellae* isolated by clinical and local public health laboratories in the state. Although it is not legally required that isolates be sent to the State Health Department, many specimens are sent in for typing. In 1969, 1,904 cases of Shigellosis were reported and 813 *Shigella* isolates were received for typing; and in 1970, the figures were 1,899 cases and 824 isolates for typing. Twenty isolates of *Shigella dysenteriae* type 1 were identified or confirmed at the Microbial Diseases Laboratory from specimens received in 1969 and 1970. Seven of these isolates were sent to the CDC in Atlanta for antibiograms.

County Health Officers in whose jurisdictions these 20 patients resided assisted in the administration of a questionnaire prepared at the State Bureau of Communicable Disease Control. Information was obtained directly from the patients or their families, from review of their hospital charts, or both. Obtained were demographic data, dates of onset and culture, travel history, circumstances of infection, résumé of symptoms, clinical course, treatment and any evidence of secondary spread.

Results

Clinical and Laboratory Features

All patients had acute enterocolitis of moderate to pronounced severity. Information regarding specific symptoms was not uniformly recorded for all 20 patients. Among 14 having a record of diarrhea, bloody diarrhea was reported in 12. Sixteen required treatment in hospital. Two were treated as out-patients, and whether

TABLE 1.—*Sensitivity in Vitro to Antibiotics* for Seven Strains of Shigella dysenteriae Type 1 Isolated in California, 1969-1970*

Antibiotic	Resistant	Sensitive
sulfathiazole	7	
cephalothin		7
tetracycline	5	2
gentamicin		7
streptomycin	7	
colistin		7
kanamycin		7
ampicillin		7
chloramphenicol	7	

*Sensitivity testing by the Kirby-Bauer method.⁴

the other two were treated in or out of hospital is unknown. Of the 16 admitted to hospital, the length of stay is known for seven; the range was from 3 to 44 days, with a median of 7 and a mean of 9.8 days. Complications included one case of hemolytic uremic syndrome in a 4-year-old girl, who recovered. Another 4-year-old girl died after 44 days in hospital with an illness characterized by bloody diarrhea, fever, abdominal cramps, edema, malnutrition and concurrent *Trichuris trichiura* infestation.

Antibiogram testing of seven isolates at the CDC revealed that all were sensitive to ampicillin and all were resistant to sulfathiazole, streptomycin, and chloramphenicol. Only two of the seven were sensitive to tetracycline (Table 1).

Epidemiologic Features

Nine of the 20 patients were under 10 years of age; the sex distribution was equal. Ten cases were reported from Los Angeles County and six from San Francisco (Table 2). Thirteen of the 20 patients had Spanish surnames. Dates of onset of illness showed a peak in the third quarter of 1970 (Chart 1).

Eighteen of the 20 patients had histories of travel in Mexico or Central American countries just before or concurrent with the onset of illness. Specific locations are given in Table 3. Only one case was associated with travel to a country outside the western hemisphere (Afghanistan). Noteworthy is that widely scattered areas throughout Mexico were implicated by 12 travelers to that country. One of the patients who had onset of symptoms in Acapulco may have been infected by a woman recently arrived from Guatemala who prepared foods for him in a pri-

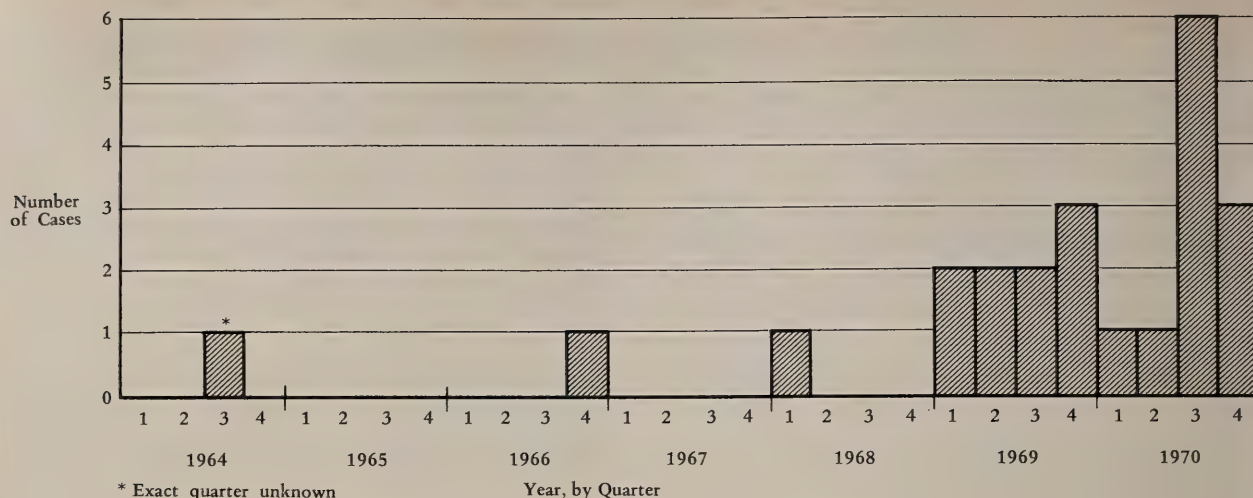


Chart 1.—Cases of *Shigella dysenteriae* Type 1 in California by Onset of Illness, 1964-1970.

TABLE 2.—Cases of *Shigella dysenteriae* Type 1 by County of Residence in California, 1969-1970

County	No.
Los Angeles	10
San Francisco	6
San Diego	1
Santa Clara	1
San Mateo	1
Orange	1
Total	20

TABLE 3.—Cases of *Shigella dysenteriae* Type 1 by History of Foreign Travel*—California, 1969-1970

Mexico**	12
Guatemala	4
El Salvador	2
Afghanistan	1
No travel	1
Total	20

*During or just before onset of symptoms.

**Areas of travel included Tijuana, Mexico City, Acapulco, Guadalajara, Isla Mujeres, Isla de Cozumel, Michoacán State, and Jalisco State.

vate home. Also of special interest is the 18-month-old Mexican-American girl from Los Angeles who had reportedly never been outside the United States. The source of her illness remains unknown. Her father works as a maintenance man in San Diego, where he was reported to clean toilets barehanded with steel wool. He drives to Tijuana almost daily and regularly visits his family in Los Angeles on weekends. He was unavailable for enteric cultures at a time

when all others in his family were negative for *Shigella*. Another contact of this child was her baby-sitter who had arrived from Mexico a few months before the onset of illness in the child. The baby-sitter had no known diarrheal illness and a stool culture was negative for pathogens.

There was no laboratory or epidemiologic evidence of secondary transmission of *S. dysenteriae* type 1 from any of 12 patients on whom such information was available.

Discussion

Shiga dysentery has been a rare disease in modern times. Since the initial description of it in 1898,⁵ it has been noted for its unusual virulence. Before World War I, outbreaks with high morbidity and mortality were reported from most continents. Since 1920, however, epidemic activity of this microbe has virtually ceased, for reasons unknown.⁶ Factors believed responsible for its apparent disappearance have included improved environmental sanitation, personal hygiene, and nutrition.⁷ Other *Shigellae*, especially *S. sonnei*, have replaced the Shiga bacillus, particularly in urban areas.⁸ Since 1920, Shiga's bacillus has been isolated only on rare occasions in Central America, both from isolated regions and from some major population centers.⁷ It appears, then, that Shiga's bacillus was endemic in Central America at a very low level before the recent epidemic. The reasons for its reemergence in epidemic proportions in this area of the world are unknown, but Mata et al have speculated on the contribution of several factors: rapid

growth and increased mobility of the population, primitive sanitation essentially unchanged for decades, polluted water supplies, and severe climatic conditions in 1969 of unusually high temperatures with drought, followed by flooding.⁷ The lone case in this series with a presumed source in Afghanistan probably reflects the low endemicity of *S. dysenteriae* type 1 in other areas of the world.

The last reported outbreak of dysentery due to Shiga's bacillus in the United States occurred among a group of Mexican migrant workers in Michigan in the summer of 1938.⁹ The disease was quite virulent, killing 10 of 45 patients for a case fatality rate of 22.2 percent. All deaths were in children less than 8 years of age.

Of public health concern has been the importation of Shiga dysentery from the recent outbreak in Central America to poverty areas in the United States, with the establishment of new epidemic foci. A single secondary case has been reported in New Mexico,¹⁰ but no definite secondary transmission could be documented by our review of California cases. The one child who had never been outside of the United States may represent a secondary case from contact with someone returning from Mexico.

It is probable that the 20 isolations of *S. dysenteriae* type 1 identified at the state laboratory in 1969-1970 represent only a small fraction of the cases actually occurring. First, some physicians do not routinely order stool cultures on patients with diarrhea or even dysentery. Second, this organism is difficult to culture on classic *Salmonella-Shigella* (s-s) agar.⁷ Third, even if *S. dysenteriae* type 1 is successfully isolated at local laboratories, there is no requirement for submission of *Shigella* isolates to the state laboratory as there is for *Salmonella* isolates.

Since our cases were selected from bacteriologic reports, our finding of significant morbidity (as indicated by admission to hospital) in a high proportion of cases should not be surprising. Retrospective studies are usually weighted by the most seriously ill.

Shiga dysentery may be confused with amebic dysentery, other types of shigellosis, salmonellosis, ulcerative colitis, and regional enteritis. The early impression in Central America that an outbreak of amebic dysentery was rampant probably contributed to the initial high mortality

through the use of toxic anti-amebic drugs.² The isolation of *Entameba histolytica* from a patient with dysentery after travel to Central America or Mexico may at times merely represent a carrier state, and other causes of dysentery such as *S. dysenteriae* type 1 need to be ruled out. The bacteriologic examination of fresh stools is essential. In the 1938 outbreak in Michigan, no isolations were made from preserved portions of stools which had been found to be "teeming with dysentery bacilli" in the fresh state.⁹ Mata et al⁷ recommended that fecal specimens be cultured promptly at the bedside or in the field with freshly prepared media. If transport media must be used, preliminary studies indicate that Cary-Blair or buffered glycerol saline solution may be best.¹¹ In a recent study of selective and differential media for the isolation of Shiga's bacillus, XLD, MacConkey's, and Tergitol-7 agar gave the best results, EMB medium gave intermediate results, and s-s agar gave the poorest results for primary isolation.¹²

Strains of *S. dysenteriae* type 1 isolated during the 1969 epidemic in Guatemala have shown multiple antibiotic resistance.⁷ Resistance *in vitro* to sulfathiazole, tetracycline, streptomycin, and chloramphenicol was reported in 52 of 53 strains studied. Yet these agents are sometimes selected as first-line drugs in dysentery cases before isolations and sensitivity results are obtained, if obtained at all. All 53 strains showed *in vitro* sensitivity to ampicillin, with 100 percent sensitivity also reported for cephalothin, gentamicin, colistin, kanamycin, nalidixic acid, and nitrofurantoin. It would appear that ampicillin is the agent of choice for infection with Shiga's bacillus. It has proved useful in the treatment of shigellosis of various serotypes when compared with untreated controls and with a group treated with parenteral kanamycin.¹³ Only the ampicillin group showed significant reduction in the duration of abdominal cramps, diarrhea, and fever.

Once a case of Shiga dysentery is identified in this country, prompt epidemiologic investigation is essential to identify potential sources of infection, to identify other patients and arrange for their treatment, and to institute control measures to limit potential spread. The high virulence of this particular *Shigella* serotype, especially in children, cannot be overemphasized. Dysentery in a recent traveler to Mexico or

Central America should be considered Shiga bacillus dysentery until proved otherwise, and managed accordingly.

ADDENDUM: During 1971 the incidence of *S. dysenteriae* type 1 increased in California: 15 additional isolates of this pathogen were identified at the state's Microbial Diseases Laboratory. Of 14 patients for whom travel histories are known, three did not travel outside of California; the remaining 11 visited Mexico shortly before onset of symptoms. Eleven required admission to hospital, one was treated as an outpatient, and no information was available on three. Laboratory studies documented intrafamily transmission in one case. Complications included apparent disseminated intravascular coagulopathy in two cases—one with acute renal failure and the other with bloody diarrhea, hematuria, epistaxis, and convulsions. A third child died. These events emphasize the extraordinary virulence which *S. dysenteriae* type 1 has for children.

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Philip, Orange County Health Department. Dr. Karl Western, Los Angeles County-USC Medical Center, provided clinical information. Miss Florence Morrison of the state's Bureau of Communicable Disease Control assisted in the preparation of the manuscript.

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COMBATING ALKALINITY IN VAGINITIS

Normally the vagina is acid in reaction, and this healthy acid reaction is what keeps yeast, fungi, and bacteria from overgrowing. Unfortunately the menstrual blood is alkaline. . . . So every month every girl lowers her barrier. Sometimes simply having a prolonged flow is enough to produce vaginitis. . . . It's important that you explain to the patient the need to establish and keep this normal healthy acid reaction.

In general for bacterial vaginitis we use Baculin® suppositories; for the yeast variety we usually give Mycostatin® in one form or another; and for the trichomonads we give both partners Flagyl® and ask the husband to use a condom.

We also suggest that for the next six periods at least the patient acidify herself after her flow is over with acid douches. . . . You may remember that some years ago 4 tablespoons of vinegar in a quart of water was agreed upon as the normal acidity of the vagina—pH of 4.3 to 4.7. . . . The patient can douche sitting on the toilet by closing the labia around the douche nozzle so the water won't run back. Fill the vagina and hold it for several minutes so that the folds are smoothed out. This makes the douche a treatment rather than a simple irrigation. Also if you have a patient who is very uncomfortable you can make her very comfortable almost immediately by having her use a Tampax®.

—ROBERT N. RUTHERFORD, M.D., Seattle
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Medical Progress

Multiple Sclerosis

Current Etiological Concepts

FREDRICK J. SEIL, M.D., Palo Alto

■ *An animal model for acute multiple sclerosis (MS) is experimental allergic encephalomyelitis (EAE). EAE is produced by intradermal injection of a protein component of central nervous system (CNS) myelin. Ultrastructural studies of EAE and of a peripheral nerve analog, experimental allergic neuritis (EAN), have revealed an orderly sequence of cellular events leading to the destruction and removal of myelin with sparing of axons (primary demyelination). Acute MS has not been studied electron microscopically, but the ultrastructural similarities between EAN and a case of acute Landry-Guillain-Barré syndrome, a primary demyelinating disease of the peripheral nervous system, suggest that a similar sequence of events might be found in acute MS. While the pathological findings support a cell-mediated or delayed hypersensitivity response, there is also evidence for the pathogenetic role of circulating antibodies. Among such evidence is included the finding that sera from animals with EAE and humans with acute MS rapidly produce a reversible block of complex (polysynaptic) electrical activity when applied to CNS tissue cultures, which suggests a possible mechanism for transient symptoms in MS. Epidemiological and other studies link MS with a viral cause, although no direct evidence that MS is caused by a virus exists. Viral and immunological mechanisms are not mutually exclusive in considering pathogenetic possibilities for MS, for it can be postulated that a viral infection of the central nervous system acts as a triggering agent for a series of immune responses, including production of a bioelectric blocking antibody and demyelination mediated by sensitized cells, the combination of which ultimately produces the total clinical picture of MS.*

Reprint requests to: F. J. Seil, M.D., Neurology Department (Stanford Service), Veterans Administration Hospital Division, 3801 Miranda Avenue, Palo Alto, Ca. 94304.

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AS TWO COMPREHENSIVE reviews of experimental work related to multiple sclerosis (MS) have recently been published,^{1,2} the purpose of this report will be to highlight some aspects of research directed at the etiology of MS. In particular, studies dealing with the animal model, experimental allergic encephalomyelitis (EAE), and those employing the nerve tissue culture technique will be emphasized. In view of the attention attracted by the possibility of a viral cause for MS,¹⁻³ some consideration will be given to the conceivable role of a virus.

Experimental Allergic Encephalomyelitis

Experimental allergic encephalomyelitis is an inflammatory disease of the central nervous system (CNS) induced in animals by injection of normal CNS tissue of either the same or of a different species, usually in the company of Freund's complete adjuvant.^{4,5} An animal's own brain tissue could as well serve as the antigen.¹ The disease is characterized clinically by weight loss, ataxia and paralysis of the limbs, and pathologically by perivenular infiltration of the CNS by mononuclear cells and demyelination.^{5,6} The pathologic changes of the acute phase of the disease resembles, at the light microscopic level, the changes of human postvaccinial encephalomyelitis, postinfectious encephalomyelitis and acute MS; hence EAE has been considered to be an animal model for these human diseases.⁷ If B. pertussis is substituted for M. tuberculosis in the preparation of Freund's adjuvant, a "hyperacute" form of EAE is produced, characterized by rapid clinical onset, necrosis of vessel walls and perivascular hemorrhages, infiltrates of mononuclear and polymorphonuclear leukocytes and demyelination.⁸ The hyperacute form of EAE has been regarded as an animal model of human acute necrotizing hemorrhagic encephalopathy.¹ If peripheral nervous system (PNS) tissue is substituted for CNS in the preparation of the antigenic material, pathologic changes similar to EAE are confined to peripheral nerves and nerve roots.⁹ This experimental animal disease, experimental allergic neuritis (EAN), has been regarded as a model system for the Landry-Guillain-Barré syndrome.^{10,11}

While the specific antigenic factors in PNS remain to be elucidated, it has been found that a protein fraction of CNS myelin which migrates toward the cathode on electrophoresis is enceph-

alitogenic.¹² Small doses of this myelin basic protein (BP), given with Freund's complete adjuvant, produce a clinical and pathological picture of EAE identical with that produced by larger doses of whole CNS.¹³ The amino acid sequence of myelin basic protein, which constitutes at least 30 percent of the total myelin protein,¹⁴ has been determined for human and bovine basic protein.² The whole molecule of 170 amino acids has been further fractionated, with encephalitogenic activity having been found with a peptide consisting of a linear sequence of nine amino acids, and an encephalitogenic peptide containing 11 amino acids has been synthesized.¹⁵

Pathological Aspects of EAE and MS

The essential pathological lesion in both EAE and EAN is primary demyelination, by which is meant the destruction of myelin with sparing of the axon.⁷ Electron microscopic studies have revealed an orderly sequence of events leading to the destruction and removal of myelin sheaths, common to both EAE and EAN.^{13,16-19} The pathological changes in EAE and EAN are so similar that these two disease models may be considered together.

Before further discussion of the pathological events, it might be well to briefly review some of the pertinent ultrastructural features of myelin. PNS myelin is formed by the concentric wrapping of peripheral axons by Schwann cell cytoplasmic membranes.²⁰ Each myelinated segment, or internode, is formed by a single Schwann cell. The central myelin forming cells are the oligodendrocytes.²⁰ Each oligodendrocyte contributes to the myelin of several central axons, and therefore is involved in the formation of at least several internodal segments. As the processes of myelin-forming cells become wrapped around axons, cytoplasm is extruded, resulting in apposition of the inner surfaces of the cytoplasmic membranes with consequent formation of the major dense lines of the myelin sheaths. Apposition of the outer surfaces of the encircling cytoplasmic membranes results in formation of the minor dense or intraperiod lines. The electron microscopic picture of a myelin sheath thus consists of a repeated pattern of alternating dark osmiophilic major dense lines and less heavy minor dense lines, separated from each other by non-osmiophilic light intervals. It is believed

that the major and minor dense lines represent the protein elements of the myelin sheath, while the light zones represent the lipid elements.²⁰

The process of demyelination in both EAE and EAN begins with the traversing of the walls of venules in the nervous system by mononuclear cells, which are believed to be transformed lymphocytes.^{18,21,22} The mononuclear cells pass from the vascular lumen either through or between endothelial cells and subsequently penetrate the vascular basement membrane.^{18,22} In the CNS the next step is the surrounding of myelin sheaths by invading mononuclear cells or their processes (Figure 1,A), while in the PNS this is accomplished after penetration of the Schwann cell basement membrane and separation of the Schwann cell from the myelin sheath.¹⁶⁻¹⁹ The next and possibly key step according to Lampert^{18,19} is a vesicular myelinolysis, with splitting of the myelin lamellae along major dense lines (Figure 1,B). Subsequently phagocyte cell processes, which may originate from the mononuclear cells causing the vesicular myelinolysis or from other "nonsensitized" mononuclear cells, invade the myelin sheaths at points of lysis (Figure 1,C), progressively peel myelin lamellae along minor dense (intraparallel) lines, and remove and digest the resultant myelin debris^{13,16-19} (Figure 1,D). Vesicular myelinolysis is not always observed however, and processes of phagocytic mononuclear cells invade myelin lamellae at nodes of Ranvier or via the outer glial loops without preceding lysis.^{13,16-19} Axons are usually spared in this process, being only occasionally secondarily involved, so that the end result is a normal-appearing axon completely stripped of its myelin (Figure 1,E). In EAN, Schwann cells are neither destroyed nor do they participate in myelin removal, contrary to their behavior in Wallerian degeneration or experimental diphtheritic neuropathy, in which damaged myelin is initially taken up by Schwann cells.^{19,23} In EAE, oligodendrocytes may be destroyed, but the fate of these cells has not been definitely established.¹⁸

That a similar sequence of events may occur in human demyelinating disease was demonstrated by an ultrastructural study of a patient with the Landry-Guillain-Barré syndrome who died during the acute phase of the illness.¹¹ The findings on electron microscopic examination of peripheral nerves and nerve roots included mye-

lin destruction with axonal sparing, a vesicular myelinolysis associated with macrophages or mononuclear cells and a failure of Schwann cells to participate in myelin phagocytosis, which was accomplished by macrophages. The pathological picture was very similar to that seen in EAN. To date, no case of MS has been studied electron microscopically in the acute phase. Those MS lesions which have been studied at the ultrastructural level have all been chronic,²⁴⁻²⁶ and the pathological features are comparable to those seen in chronic EAE.²⁷ The acquisition of tissue in an appropriately acute stage of MS and in a state of preservation adequate for the type of detailed ultrastructural examination that has been performed in animals with EAE will require an extraordinary set of circumstances. Thus there may be some interval of time before comparisons can be made between the acute lesions of MS and EAE.

Immunological Aspects of EAE and MS

One reason for pursuing a comparison between EAE and MS relates to the consideration that MS may be an "immunological" disease. EAE clearly follows injection of an antigenic protein component of myelin, and the sequence of pathological events suggests a cell-mediated or delayed hypersensitivity type of response, with the essential steps appearing to be invasion of the nervous system by sensitized cells and the encirclement and lysis of myelin sheaths, which occurs in the presence of mononuclear cells.¹⁸ The phagocytic stripping of myelin lamellae which follows is a non-specific reaction which can be seen in conditions other than EAE.²⁸ The finding of a similar sequence of cellular events in acute MS could suggest that similar immune mechanisms play some role in its pathogenesis.

While the described pathological events in EAE suggest a delayed hypersensitivity response, there is considerable controversy as to whether EAE induction is cell-mediated or whether circulating antibodies participate in the development of the CNS lesions. Additional evidence in favor of the delayed hypersensitivity concept includes the fact that EAE can be passively transferred from diseased to healthy animals by injection of lymph node cells^{29,30} or whole blood,³¹ while such passive transfer is not possible by either intraperitoneal or intravenous injection of se-

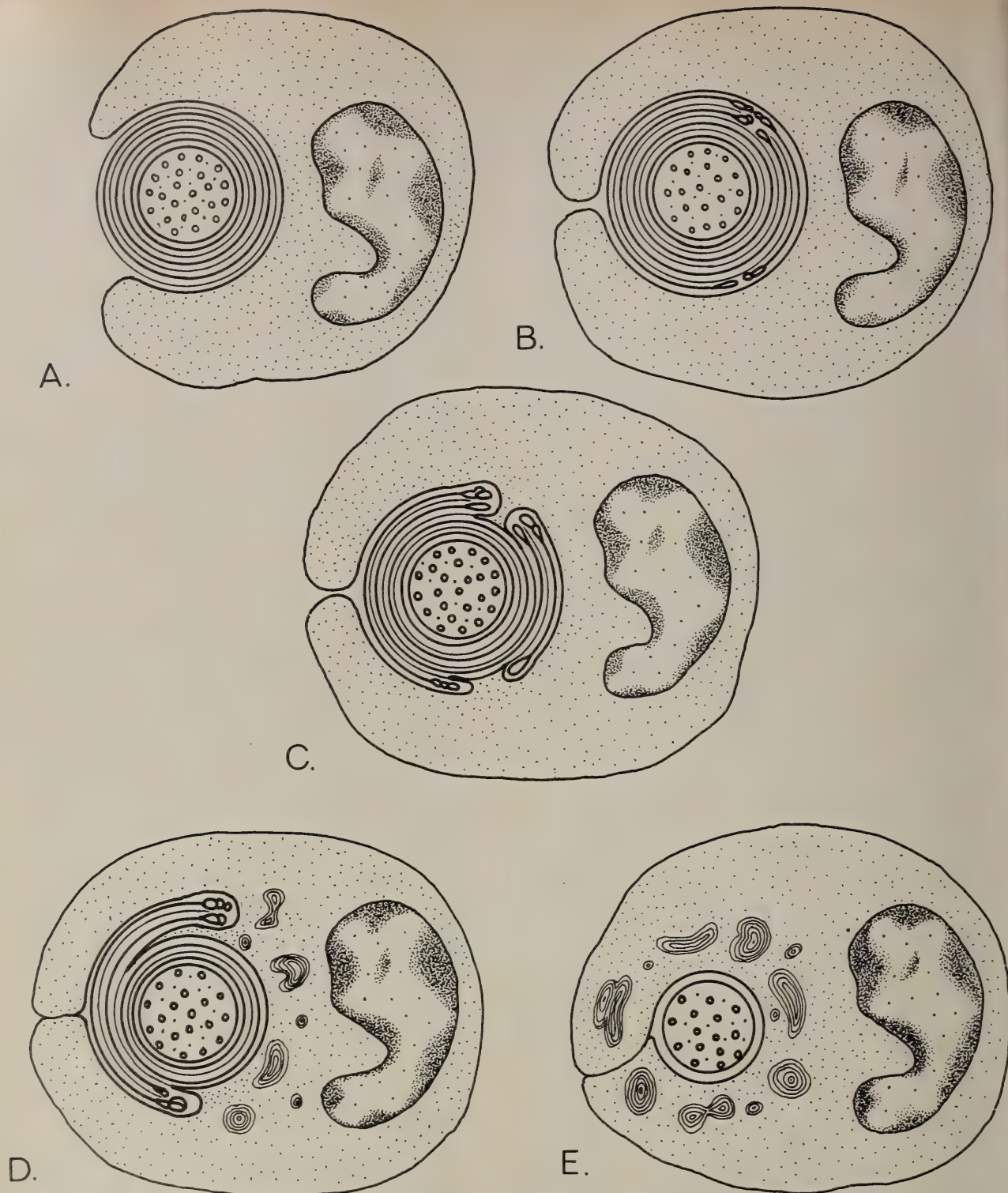


Figure 1.—Semi-schematic illustration of cell-induced myelinolysis and subsequent myelin lamellar stripping as occurs in EAE and EAN, based on electron micrographs by Lampert (see text for references). A, a myelinated axon is surrounded by an invading mononuclear cell of hematogenous origin. B, vesicular myelinolysis occurs in the presence of the "sensitized" mononuclear cell, with splitting of the myelin lamellae along major dense lines. C, mononuclear cell processes invade the myelin sheath at points of lysis and begin to separate myelin lamellae along minor dense (intraparallel) lines. D, at a more advanced stage myelin lamellae are progressively peeled, with phagocytosis of the resultant myelin debris. E, the end result of this process is a normal-appearing axon completely stripped of its myelin, with myelin debris continuing to undergo phagocytosis.

rum.³² Also consistent with cellular hypersensitivity is the correlation of delayed skin reactions to basic protein (BP) with the induction of disease.³³ Skin reactions after injection with BP reach a peak a few days before onset of EAE, and subsequently decrease as signs of EAE develop. This has been interpreted to mean that the lymphoid cells which have been involved in the delayed skin reaction are withdrawn from the periphery by subsequent attraction to the antigen in the CNS, where they then produce delayed hypersensitivity reaction of the same type.²

Other supportive data favoring delayed hypersensitivity as the pathogenetic mechanism of EAE include the presence of low titers or absence of circulating anti-BP antibodies in guinea pigs with EAE produced by a single injection of BP in Freund's adjuvant,³⁴ and the presence of cell-migration inhibition when macrophages from EAE animals are exposed to either whole CNS or BP.^{35,36} The latter is tested by packing peritoneal exudate cells (lymphocytes plus macrophages) collected from sensitized animals into capillary tubes and maintaining them in a suitable medium. The addition to the medium of the antigen to which the animal has been sensitized results in an inhibition of the migration of macrophages from the open end of the capillary tube. The inhibitory factor is believed to be produced by sensitized lymphocytes, and the purpose of such a factor may be to keep macrophages at the antigenic site in order to perform their function of phagocytosis.^{2,37} The test is currently under evaluation as a possible investigative and diagnostic tool in MS and the Landry-Guillain-Barré syndrome.^{37,38}

Evidence which favors the role of circulating antibodies in EAE induction includes the ability of serum from animals with EAE to produce periventricular demyelinating lesions when injected directly into the ventricles of normal animals,³⁹ the finding of deposition of γ -globulin in the CNS before the appearance of cells in EAE,⁴⁰ and the ability of serum from animals with EAE produced by sensitization with whole CNS to demyelinate CNS tissue cultures.⁴¹ The tissue culture demyelinating factor was shown to be complement dependent and was localized in the 7S γ 2-globulin fraction.⁴² It could be absorbed out by previous exposure to CNS tissue, and immunofluorescent studies demonstrated attachment of the globulin to myelin sheaths and glial cell

membranes during demyelination.⁴² The presence of this demyelinating antibody in the sera of EAE animals provides a link with MS, for a high proportion of sera from acute cases of MS also demyelinated CNS tissue cultures.^{43,44} In both instances, removal of the demyelinating serum and return of the cultures to their normal nutrient medium was followed by remyelination.⁴³ On the other hand, chronic exposure of cultures to high doses of EAE serum resulted in an irreversible state of "sclerosis."⁴⁵

Electron microscopic examination of cultures exposed to EAE sera revealed a selective degeneration of oligodendrocytes.⁴⁶ It was further demonstrated that if CNS cultures, which are usually derived from fetal or newborn animals before myelination, were exposed to low concentrations of EAE serum from the day of explantation on, the formation of myelin *in vitro* was inhibited and oligodendrocytes failed to differentiate.⁴⁷ Upon withdrawal of the EAE serum and replacement with normal nutrient medium, differentiated oligodendrocytes appeared and myelin was formed.

The relevance of these studies to the pathogenesis of EAE is opened to question by the demonstration that substitution of either a diffusible encephalitogenic peptide⁴⁸ or myelin basic protein⁴⁹ for whole CNS as the disease-producing antigen resulted in failure to produce tissue culture demyelinating antibody. In the latter study,⁴⁹ steps were taken to insure high levels of circulating anti-BP antibody, including sensitization with large doses of a high molecular weight BP and hyperimmunization. Hyperimmunized or "protected" animals are produced by sensitization at intervals with BP in Freund's incomplete adjuvant (without M. tuberculosis), followed by a challenge dose of BP in complete adjuvant. These animals do not develop EAE, but do exhibit high titers of anti-BP antibodies. None of the sera with high levels of anti-BP antibodies demyelinated CNS tissue cultures, indicating that antibodies to the encephalitogenic BP were not responsible for demyelination *in vitro*. The conclusion drawn from this study was that the demyelinating antibody present in the sera of whole CNS-sensitized animals was formed in response to an antigen not involved in the pathogenesis of EAE, as whole CNS contains a multiplicity of antigens which are not encephalitogenic.² A dissenting note is a study which claimed that demyelinating antibody

was found in the sera of BP-sensitized animals, though in a smaller percentage than with whole CNS sensitization.⁵⁰

Similar doubts have been raised about the significance of demyelinating antibody in MS.^{1,2} Although the highest proportion of demyelinating sera have been reported in cases of active MS, tissue culture demyelinating activity has also been found in some normal sera, in sera from two cases of cobalt-irradiated brain tumors and in a high percentage of cases of amyotrophic lateral sclerosis,⁵¹⁻⁵² in which demyelination is secondary to axonal degeneration rather than primary. The presence of demyelinating antibody in conditions involving degeneration of myelin rather than primary demyelination raises the possibility that such antibody represents a nonspecific response, perhaps to the breakdown of myelin, and is not a causative factor in disease production.

Of perhaps greater relevance than demyelinating antibody to the pathogenesis of both EAE and MS is the observation that sera from animals with EAE and humans with MS abolished evoked complex electrical activity in tissue cultures soon after application.⁵³ The effect was rapidly reversible after replacement of the test sera with normal nutrient medium. A similar phenomenon was demonstrated upon application of MS sera to isolated frog spinal cord.⁵⁴ In both instances complex activity indicative of transmission over polysynaptic pathways was affected, but the assumption that the block occurs at the synaptic level remains to be proven by intracellular recording. A dissociation between demyelinating antibody and the factor blocking complex bioelectric activity is evident from a study which confirmed the absence of demyelinating activity in the sera of a majority of animals sensitized with encephalitogenic protein and demonstrated that these negative sera still blocked polysynaptic evoked responses.⁵⁵

Electron microscopic examination of tissue cultures exposed to EAE sera was reported to reveal a 30 percent reduction in the total number of synapses present after 24 hours, and a 50 percent reduction after six days of exposure.⁵⁶ These effects were reversible after return of the cultures to normal nutrient medium. The statistical difficulty with such a study, especially when there is variation from culture to culture normally, is monumental. Furthermore, the func-

tional blocking effects were present minutes after application of the test sera, long before any morphological changes, either of myelin or synapses, were evident.⁵¹ The significance of the report of morphologically altered synapses is, therefore, not entirely clear.

The significance of the functional blocking activity exhibited by EAE and MS sera may, however, be profound. It has always been difficult to explain the commonly observed transient visual, sensory and motor deficit phenomena of MS on the basis of such pathological mechanisms as demyelination and remyelination. Furthermore, the degree of clinical involvement and the extent of histological lesions in animals with EAE do not always correlate.^{57,58} A factor such as a functional blocking antibody, operating in addition to and independently of the factors causing demyelination, could provide a plausible explanation for these clinical and laboratory phenomena. Whether the functional blocking agent is an antibody or not is unclear, although the fact that it is complement-dependent⁵³ suggests that it is.

The consideration that more than one pathogenetic mechanism may underlie the clinical and histological events of EAE could bring together the opposing schools of delayed hypersensitivity versus circulating antibody. It is possible that both have a role in evoking the full picture of EAE. Such a concept is supported by the finding that maximum immunofluorescent staining of lymph node cells from EAE animals for γ -globulin occurred at a time interval after sensitization different from that when the cells exhibited maximum ability to passively transfer the disease.⁵⁹ It is conceivable that the acute clinical manifestations of EAE are produced by a functional blocking antibody, while the demyelination is a manifestation of a delayed hypersensitivity reaction. A similar line of reasoning might be applied to MS.

Viruses as Etiological Agents

Epidemiological studies of MS have indicated increased incidence of the disease in temperate climates and among the upper socio-economic classes of the more developed countries, a notable exception being Japan, where the incidence is low.⁶⁰ Studies of immigrant populations from areas of high incidence to areas of low incidence have demonstrated a prevalence rate of MS con-

sistent with that of the country of origin. Thus, while the disease is rare in native-born white South Africans, the occurrence rate is significantly higher among European-born white South Africans, and the prevalence of MS in various groups migrating to Israel correlates with the prevalence in their countries of origin with regard to both higher and lower incidence than among native-born Israelis.^{60,61} Such data, plus the long delay in onset of MS after immigration, have been interpreted as being consistent with a viral cause, the virus in question being one with an incubation period measured in years.^{60,62}

That viruses which have long incubation periods and are infective for extended periods (so-called "slow" viruses) may be involved as causative agents in human disease is suggested by the finding of transmissible agents in two chronic, progressive neurological disorders, kuru and Jakob-Creutzfeldt disease.^{3,63,64} Kuru, which means the "shakes," is an unremitting invariably fatal disease with predominantly cerebellar symptoms that is found among the Fore tribe in New Guinea. Jakob-Creutzfeldt disease, one of the pre-senile dementias, is characterized by a rapidly progressing dementia and myoclonic jerks. Both diseases have been transmitted to chimpanzees by intracerebral injection of brain homogenates from human patients, and subsequently from chimpanzee to chimpanzee by similar inoculations.^{63,64} In each instance, the clinical disease transmitted to the chimpanzees resembled the human disease, and the two conditions were easily distinguishable in the involved animals.⁶⁴

In the first instance of transmission of kuru to chimpanzees, there was a latent period of from 18 months to four years between inoculation with human material and initial appearance of signs.⁶³ This was subsequently lowered to 12 months in chimpanzee to chimpanzee passages. In the case of Jakob-Creutzfeldt disease, onset of disease was noted in chimpanzees 12 to 14 months after inoculation with suspensions of brains from afflicted humans.⁶⁴ This incubation period was not altered by subsequent passage to chimpanzees. Virus particles have not been seen in kuru on electron microscopic examination, nor have antibodies been detected.³ Virus-like particles were seen in one of five chimpanzees with experimental spongiform encephalopathy, but the difficulty in interpreting such material in light of the isolation

of a great number of viral strains from experimental chimpanzees is discussed by the investigators.⁶⁵

Although causative agents in these conditions have not been isolated and identified, the successful transmission of these diseases from man to higher primates, even with material passed through a 220 m μ filter, is nevertheless suggestive that a viral or virus-like agent is involved.

Similar attempts have been made to transmit other chronic progressive neurological diseases of man to animal hosts, including multiple sclerosis.⁶⁶ To date, no successful transfer of MS from man to higher primates by intracerebral inoculation of CNS tissue has been accomplished. There is a report, however, that inoculation of Icelandic sheep with brain homogenates from a patient who died of acute MS resulted in the development of scrapie in the sheep.⁶⁷ Scrapie is a naturally occurring disease of sheep which can be transmitted by intracerebral inoculation of filtered homogenates of CNS from affected animals to healthy sheep and to other species as well, including goats, hamsters, rats and mice.³ The incubation period of scrapie in sheep ranges from nine months to four years. Clinically affected animals develop weakness, ataxia, tremors and hyperexcitability or lethargy, while pathological changes in the CNS are similar to those found in kuru and Jakob-Creutzfeldt disease.^{3,65,68} The report of production of this disease by inoculation of tissue from a patient with MS is therefore of considerable interest. However, this study remains to be confirmed and it needs to be more clearly established that a latent natural infection was not incited by the experimental procedures.

Other findings suggestive of the possible etiologic role of viral agents in MS include the presence of higher viral antibody titers in the sera of MS patients than in the sera of matched controls. This was true for measles, type C influenza, herpes simplex, parainfluenza 3, mumps and varicella-zoster.⁶⁹⁻⁷⁰ Such studies, however, by no means provide a direct relationship between viruses and MS, as the authors reporting these data readily admit.⁷⁰ Thus, while there are a number of suggestive links between viruses and MS, the relationship of these agents to the disease can be summarized by the statement that there is at present no direct evidence that MS is of viral origin.

Virus and Immune Mechanisms Combined

The possibility of a viral factor and the possibility that immunological mechanisms play a prominent role in the pathogenesis of MS are not mutually exclusive. Unlike the animal model, EAE, and unlike human postvaccinal encephalomyelitis, both of which are produced by intradermal injection of CNS tissue, no such direct exposure to an antigenic agent is known to exist in MS. If MS is an immunological disease, some triggering event is required to set the immunopathogenetic mechanisms in motion. A viral infection of the CNS could conceivably play such a triggering role, as has been suggested previously,¹ by causing a breakdown of some myelin with resultant release of encephalitogenic proteins or peptides. The response to the presence of the released encephalitogens might be the production of a functional blocking antibody and the sensitization of lymphocytes. The former might be responsible for acute, transient deficit phenomena while the consequence of the latter would be a cell-mediated demyelinating reaction, with the combination of these factors ultimately producing the total clinical picture of MS.

What causes MS remains unknown. Some progress has been made toward understanding possible pathogenetic mechanisms underlying MS and other demyelinating diseases, but much remains to be learned. The point of continuing to pursue studies such as those described in this review is eventually to provide a rational basis for therapy, a need evidenced by the almost annual appearance of a new "cure" for this still puzzling disease.

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MEDICAL STAFF CONFERENCE

Renal Tubular Acidosis

These discussions are selected from the weekly staff conferences in the Department of Medicine, University of California, San Francisco. Taken from transcriptions, they are prepared by Drs. Sydney E. Salmon and Robert W. Schrier, Assistant Professors of Medicine, under the direction of Dr. Lloyd H. Smith, Jr., Professor of Medicine and Chairman of the Department of Medicine. Requests for reprints should be sent to the Department of Medicine, University of California, San Francisco, San Francisco, Ca. 94122.

DR. SMITH:* The first case this morning is that of a patient with Sjögren's syndrome and renal tubular acidosis. The case history will be presented by Dr. Wooten.

DR. WOOTEN:† The patient is a 62-year-old woman who was first referred to the University of California Medical Center in 1967 for evaluation of muscle weakness. She had been well until 1957 when she was discovered to be anemic. Shortly thereafter she began to have recurrent petechiae and purpura on her legs and Raynaud's phenomenon. Subsequently, she began to note dry mouth, nocturia, and burning sensations in her eyes. In 1965, she noted the gradual onset of weakness of the lower extremities, first manifested by difficulty in rising from a seated position. By the time of her admission in 1967 she was unable to stand or walk without support.

On physical examination, the patient appeared pale and wasted. Vital signs were normal. Physical findings included reddened conjunctivae, hepatomegaly, and brownish pigmentation with interspersed petechiae over the pretibiae. Muscle tone was poor, the pelvic girdle musculature was wasted, and a striking degree of proximal muscle weakness was present. A Schirmer test was positive; a slit-lamp examination revealed degenera-

tive changes of the cornea and moderately severe keratitis, consistent with Sjögren's syndrome.

Pertinent laboratory data on admission included: hemoglobin 10.7 grams per 100 ml, white blood cell count 3,100 per cu mm, serum sodium 138 mEq, potassium 3.2 mEq, chloride 115 mEq, and total CO_2 13 mEq per liter. The serum creatinine concentration was 1.9 mg and blood urea nitrogen 18 mg per 100 ml. The arterial pH was 7.23, the urine pH was 6.8, and the urinary excretion rates of titratable acid and ammonium were greatly reduced. Serum calcium concentration was 8.9 mg, phosphorus 2.3 mg per 100 ml, and the alkaline phosphatase was 17 Shinowara-Jones-Rhinehart units (normal range 2 to 6). Laboratory studies for malabsorption syndrome were negative. Serum protein electrophoresis showed a broad based elevation in gamma globulin. The urine contained 400 mg of protein per 24 hours; glucose was not present. Cultures of the urine were negative. Twenty-four-hour urinary total alpha-amino nitrogen was greatly increased.

Following correction of the patient's acidosis and potassium depletion, her muscle strength improved greatly. Sustained correction of acidosis required administration of 200 mEq of bicarbonate daily. Despite sustained correction of acidosis, she continued to require potassium supplements

*Dr. Lloyd H. Smith, Jr., M.D., Professor and Chairman of Medicine.

†Dr. George F. Wooten, Intern in Medicine.

to maintain normokalemia. Urinary excretion of aldosterone, measured by Dr. Edward Biglieri, was increased.

The patient's inulin clearance was 25 ml per minute. At normal plasma bicarbonate concentrations, measurements of urinary bicarbonate excretion indicated that the patient excreted between 30 and 40 percent of the filtered load of bicarbonate.

Between 1967 and the present, the patient's renal function has remained essentially unchanged. Treatment with sodium phosphate supplements resulted in further improvement in her muscle strength. Renal biopsy in 1969 showed interstitial nephritis. In summary, the patient is a 62-year-old woman, who presented four years ago with Sjögren's syndrome, chronic renal insufficiency associated with renal tubular acidosis, renal potassium wasting, and Fanconi syndrome. Severe proximal myopathy responded to correction of acidosis and potassium depletion.

DR. SMITH: This morning we have asked Dr. Anthony Sebastian to discuss this patient and in particular to discuss the pathophysiology of her renal tubular disorder.

DR. SEBASTIAN:* As most of you know, metabolic acidosis is a usual consequence of chronic progressive disease of the kidney. Irrespective of cause, chronic renal disease usually results in some degree of acidosis when the degree of renal damage becomes sufficiently severe, or sufficiently extensive, to reduce glomerular filtration rate to 25 ml per minute or less. Acidosis that develops in these circumstances—so-called uremic acidosis—has generally been considered to be the consequence of a reduction in number of functioning nephrons. In certain diseases of the kidney, however, metabolic acidosis can occur even though the glomerular filtration rate is not reduced or is only slightly reduced. In these diseases, the renal tubular process of hydrogen ion (H^+) secretion may be greatly impaired in a normal or nearly normal number of nephrons. The impairment of renal acidification gives rise to a characteristic syndrome: hyperchloremia, metabolic acidosis, minimal or absent azotemia, inappropriately high urinary pH, bicarbonaturia, and reduced urinary excretion rates of acid (titratable acid and ammonium). This syndrome and the disorders of renal acidification that give rise to it have been designated renal tubular acidosis (RTA).^{1,2} The

discussion this morning will be devoted primarily to a consideration of the pathogenesis and pathophysiology of renal tubular acidosis.

Renal Acidification in Normal Subjects

The kidney participates in the regulation of systemic acid-base homeostasis by regulating the concentration of bicarbonate (HCO_3^-) in the plasma.³ Under normal physiological conditions, the action of the kidney that operates to maintain normal plasma bicarbonate concentrations can be viewed as the secretion of bicarbonate ions from renal tubular cell to plasma at a rate just equal to the rate at which plasma bicarbonate is filtered at the glomerulus plus the rate at which plasma bicarbonate and buffer bases throughout the body are titrated by the nonvolatile strong acids (chiefly sulfuric and phosphoric) produced as end-products of metabolism (Chart 1). Accordingly, in normal subjects, neither loss of bicarbonate via glomerular filtration (approximately 4,500 mEq per day) nor continuous endogenous production of nonvolatile acid (approximately 1.0 mEq per kg body weight per day) leads to the development of metabolic acidosis.

According to current concepts, bicarbonate ions secreted into the plasma by the renal tubular epithelium are generated with equimolar amounts of hydrogen ion, via hydration of intracellular carbon dioxide. The hydrogen ion generated is disposed of by secretion into the lumen (Chart 1). Physicochemical evidence from micropuncture experiments indicate that the secretion of H^+ is an active process; the secretion of HCO_3^- from cell to plasma is regarded as a passive process in which HCO_3^- diffuses along a favorable concentration gradient sustained by the secretion of H^+ into the lumen.⁴ Approximately 98 percent of the H^+ secreted into the lumen is utilized in the titration of filtered HCO_3^- to carbonic acid, which dissociates to carbon dioxide and water, and recycles. Secretion of H^+ , therefore, effects the "reabsorption" of filtered HCO_3^- by providing for the delivery of bicarbonate to the blood at a rate equal to the rate at which bicarbonate is filtered. In providing for the delivery of additional bicarbonate to the blood at a rate equal to the rate of endogenous nonvolatile acid production, the remaining 2 percent of secreted H^+ can be recovered in the urine, largely in the form of monobasic phosphate ($H_2PO_4^-$) and ammonium

*Anthony Sebastian, M.D., Assistant Professor of Medicine.

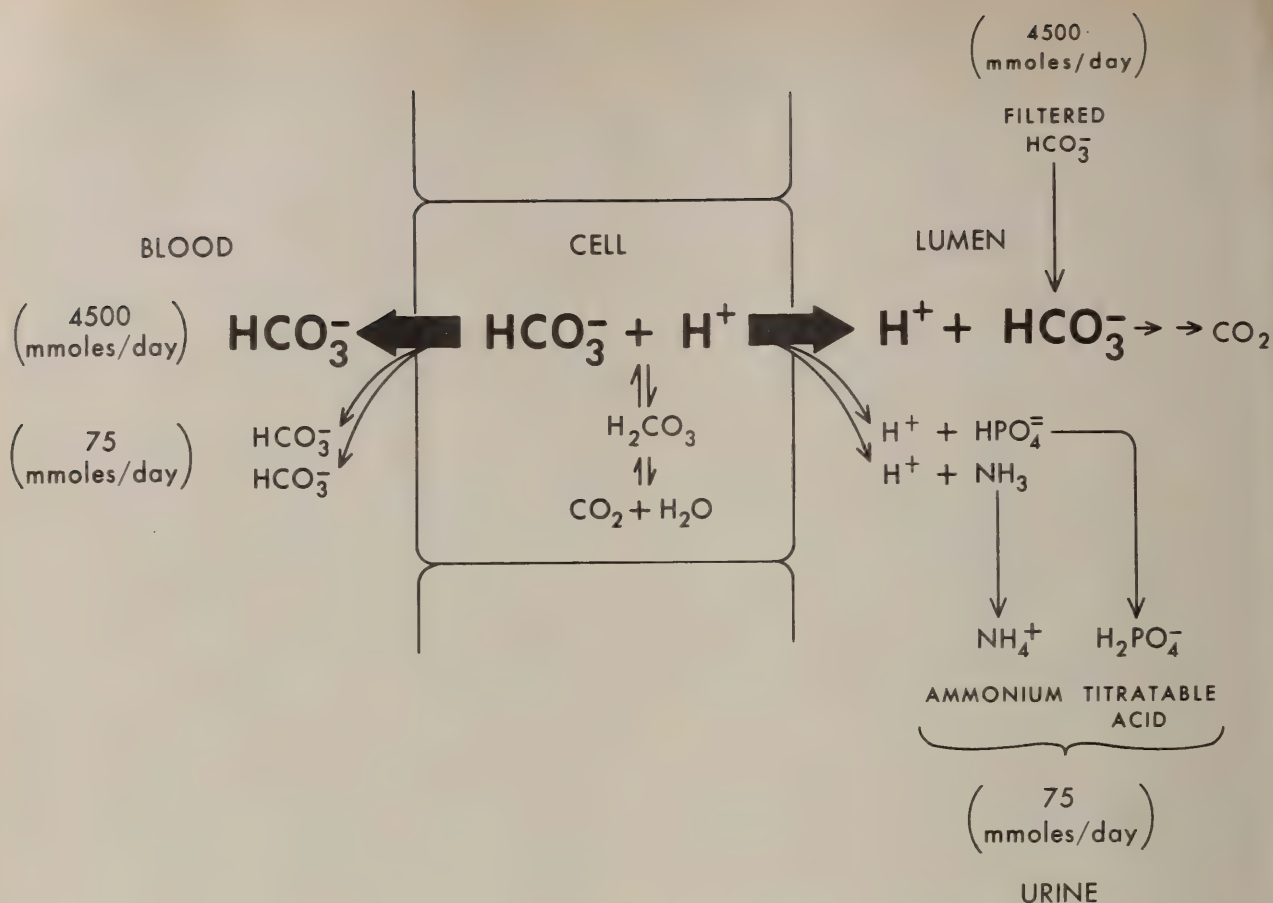


Chart 1.—Schematic representation of the renal acidification process. At normal plasma bicarbonate concentrations under normal physiological conditions, the kidney delivers bicarbonate to the blood at a rate equal to the rate at which bicarbonate is filtered at the glomerulus (4,500 mmoles per day) plus the rate at which non-volatile strong acids are produced endogenously (75 mmoles per day). Delivery of bicarbonate to the blood is associated with the delivery (secretion) of an equimolar amount of hydrogen ion into the tubular lumen, approximately 98 percent of which titrates filtered bicarbonate (4,500 mmoles per day) and about 2 percent of which is excreted in the urine as titratable acid and ammonium (75 mmoles per day).

(NH_4^+), having titrated the urinary buffer bases dibasic phosphate (HPO_4^-) and ammonia (NH_3). The amount of secreted H^+ excreted in the urine as H_2PO_4^- can be estimated by back-titration of urine with strong base to the pH of plasma, hence is referred to as titratable acid. In normal subjects under normal physiological conditions, the sum of the rates of excretion of titratable acid and ammonium equals approximately the rate of endogenous nonvolatile acid production, about 1 mEq per kg of body weight per day.

Successful operation of the renal H^+ secretory process to maintain plasma bicarbonate at normal concentrations can be viewed in terms of two interrelated requirements: (1) that the proximal portions of the nephron secrete H^+ at appropriate rates, (2) that the distalmost portions of the nephron generate and maintain appropriately

steep H^+ concentration gradients from cell to lumen. Micropuncture experiments in several mammalian species indicate that H^+ secreted in the proximal convoluted tubule titrates some 85 to 90 percent of the filtered load of bicarbonate.⁵ Since 98 percent of H^+ secreted by the renal tubule is utilized in titrating filtered bicarbonate, most of the H^+ secreted by the kidney is secreted in the proximal tubule. A reduction in the rate of H^+ secretion in the proximal nephron might therefore result in massive urinary bicarbonate loss; the corresponding reduction in the rate of bicarbonate delivery from cell to plasma would then be viewed as the proximate cause of the predictable reduction in plasma bicarbonate concentration and attendant development of metabolic acidosis.

The ability of the distalmost segments of the

TABLE 1.—Physiological Characteristics of Impaired Renal Acidification in Prototypical Type 1 and Type 2 Renal Tubular Acidosis

	Type 1 RTA (Classic RTA; "Distal" RTA)	Type 2 RTA ("Proximal" RTA)
Generation of steep H^+ gradients	impaired	intact
Minimal pH of urine	>6.0	<5.5
HCO_3^- excretion during severe acidosis	small, persisting	none
Acid excretion during acidosis	subnormal	not reduced
Secretory rate of H^+ at normal $[HCO_3^-]_p$	essentially normal	markedly reduced
HCO_3^- excretion at normal $[HCO_3^-]_p$	<3% of filtered HCO_3^-	>15% of filtered HCO_3^-

nephron to generate and maintain steep H^+ concentration gradients between cell and lumen accounts for the operation of the distal H^+ secretory process (1) to titrate completely the 10 percent or so of filtered bicarbonate that escapes titration proximally, and (2) to titrate the urinary buffer bases to such an extent that the combined rates of excretion of titratable acid and NH_4^+ approximate the rate of endogenous production of non-volatile acid. Urinary bicarbonate excretion is usually negligible when the pH of the urine is less than about 6.2. The rates of excretion of titratable acid and NH_4^+ are inversely related to urinary pH, which may vary widely (from <5.0 to >7.0) throughout the day. Daily excretion of appropriate amounts of titratable acid and NH_4^+ appears to depend upon at least occasional excretion of urine with pH values less than 6.0. An impairment of the ability of the distal nephron to generate appropriately high intraluminal H^+ concentrations might be expected to result in a reduction in urinary acid excretion and slight urinary bicarbonate loss; the corresponding reduction in bicarbonate delivery to the blood would account for the attendant development of metabolic acidosis. Theoretically, the rate of bicarbonate delivery to the blood could be reduced by as much as 10 to 15 percent of normal if the H^+ secretory process of the distal nephron were obliterated.

On the basis of this formulation, two prototypic disorders of renal acidification can be considered: (1) Type 1 RTA (classic, "distal" RTA), character-

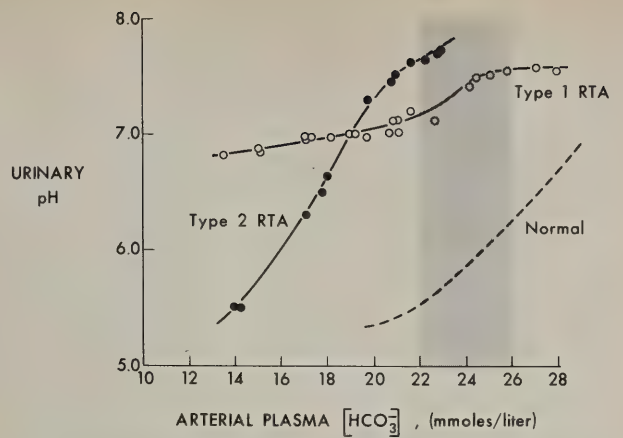


Chart 2.—The relationship between urinary pH and arterial plasma bicarbonate concentration in patients with prototypical type 1 and type 2 renal tubular acidosis. In patients with prototypical type 2 RTA, the urinary pH may be inappropriately high or appropriately low depending upon the degree of systemic acidosis. (Shaded area: range of normal plasma bicarbonate concentrations.)

ized by an impairment of the H^+ gradient-generating ability of the distalmost segments of the nephron, and (2) Type 2 RTA ("proximal" RTA), characterized by a reduction of the H^+ secretory rate of the proximal nephron (Table 1).

Pathophysiology of Type 1 Renal Tubular Acidosis

In patients with type 1 RTA, the pH of the urine remains inappropriately high (usually >6.0), and urinary acid excretion remains subnormal, throughout the day, from day to day, even if the patients are decidedly acidotic, and even if their acidosis is exacerbated by administration of exogenous acid (Chart 2). Typically, a small amount of bicarbonate is excreted in the urine (Chart 3). The amount of bicarbonate excreted, both at subnormal and at normal plasma bicarbonate concentrations—that is, before and during alkali administration—is usually less than 3 to 5 percent of the filtered bicarbonate load (Chart 3, Table 1). This finding permits the inference that the overall rate of H^+ secretion in the proximal (and distal) tubules is not greatly reduced. The observation that urinary bicarbonate excretion remains essentially constant when the plasma bicarbonate concentration is experimentally increased from subnormal to normal levels (Chart 3) is consistent with the generally inferred mechanism of the renal acidification defect, namely an inability of the distal nephron to generate ap-

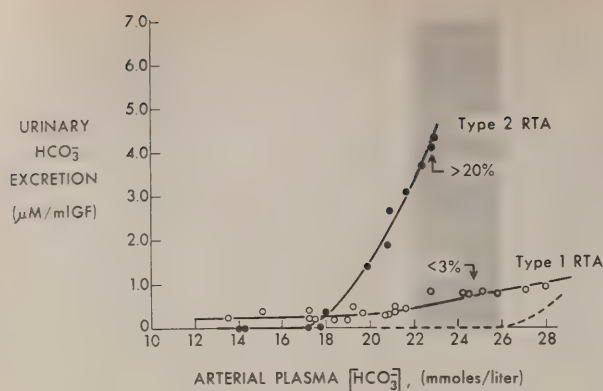


Chart 3.—The relationship between urinary bicarbonate excretion and arterial plasma bicarbonate concentration in patients with prototypical type 1 and type 2 renal tubular acidosis. In patients with type 1 RTA, the urine may contain bicarbonate even during severe degrees of acidosis, but at normal plasma bicarbonate concentrations the magnitude of bicarbonaturia is small. In patients with type 2 RTA, the urine may be bicarbonate-free during severe acidosis, but at normal plasma bicarbonate concentrations the magnitude of bicarbonaturia is large. (Shaded area: range of normal plasma bicarbonate concentrations.)

appropriately steep cell-to-lumen H^+ concentration gradients.^{1,6} Renal bicarbonate reabsorption increases when the filtered bicarbonate load is increased, presumably because the delivery of increased amounts of bicarbonate to the distal nephron raises intraluminal pH there, and thus diminishes the gradient restriction on the rate of H^+ secretion. With the simultaneous provision of a decreased concentration of intraluminal H^+ , and an increased concentration of intraluminal H^+ -acceptor (HCO_3^-), the net rate of H^+ secretion and HCO_3^- reabsorption in the distal nephron might increase whether the acidification defect involved impaired H^+ secretion per se (pump defect), increased back-diffusion of secreted H^+ (permeability defect), or both.

At normal plasma bicarbonate concentrations in patients with type 1 RTA, the disparity between the rate at which bicarbonate is delivered to the blood by the kidneys and the sum of the rates of bicarbonate filtered and endogenous acids produced is determined by both the reduction in urinary acid excretion and the rate of urinary bicarbonate loss. This disparity in turn determines the rate at which bicarbonate must be administered to maintain plasma bicarbonate concentration normal. In eleven adult patients on oral alkali therapy (venous serum

CO_2 content 26.5 ± 1.8 mmoles per liter), we found that urinary acid excretion was 0.37 mEq per kg of body weight per day and that urinary bicarbonate excretion was 0.73 mEq per kg of body weight per day.⁷ Taking 1.0 mEq per kg per day as the normal rate of urinary acid excretion, it can be inferred that the kidneys of these patients failed to deliver to the blood 0.63 mEq per kg ($= 1.0 - 0.37$), plus 0.73 mEq per kg, or a total of 1.36 mEq of bicarbonate per kg per day, at normal plasma bicarbonate concentrations. The actual amount of alkali administered to these patients to maintain normal plasma bicarbonate concentrations was 1.4 ± 0.4 mEq per kg per day, or about 60 to 150 mEq per day. In effect, administered alkali titrates endogenous non-volatile acid (1.0 mEq per kg) and replaces the *net* base (bicarbonate less acid) lost in the urine ($0.73 - 0.37 = 0.36$ mEq per kg).

Pathophysiology of Type 2 RTA

In contrast to the findings in patients with type 1 RTA, in untreated (acidotic) patients with type 2 RTA, the urine may be bicarbonate-free and appropriately acidic (for example, pH <5.5) (Charts 2, 3), and urinary acid excretion may not be reduced to rates less than the estimated normal endogenous production rate of nonvolatile acid (Table 1). Since the rate at which the kidneys deliver bicarbonate to the blood under such conditions is no greater than the sum of the rates of bicarbonate filtered and endogenous acids produced, it is not surprising that the plasma bicarbonate concentration does not increase spontaneously. The urinary findings in these patients differ from those observed in normal subjects during experimentally produced acidosis (exogenous acid loading): urinary acid excretion in such acidotic normal subjects characteristically exceeds the normal endogenous production rate of nonvolatile acid. Hence, in normal subjects when acid loading is discontinued, the plasma bicarbonate concentration increases toward normal because at first the rate of bicarbonate delivery to the plasma exceeds the sum of the rates of bicarbonate filtered and endogenous acids produced. Clearly, in acidotic patients with type 2 RTA in whom urinary acid excretion does not exceed the normal endogenous production rate of nonvolatile acid, such an increase in plasma bicarbonate concentration could not occur.

The physiological factors underlying the lower rates of urinary acid excretion in untreated patients with type 2 RTA as compared with acidotic normal subjects can be appreciated by comparing the changes in urinary pH, and in urinary acid and bicarbonate excretion, when the plasma bicarbonate concentration is progressively increased from subnormal to normal levels (in the patients, by administration of sodium bicarbonate; in the normal subjects, when exogenous acid loading is discontinued). In the normal subjects, as plasma bicarbonate concentration increases (and thus as the filtered load of bicarbonate increases), urinary pH gradually increases and urinary acid excretion gradually decreases, until at normal plasma bicarbonate concentrations the pH is neither notably acidic nor alkaline, and acid excretion is approximately normal; the urine remains essentially bicarbonate-free.³ By contrast, with similar increases in plasma bicarbonate concentration in the patients with type 2 RTA, the pH of the urine promptly increases to values greater than 7 (Chart 2), acid excretion promptly decreases to very low rates, and marked bicarbonaturia occurs (Chart 3). As the urine pH increases and acid excretion decreases with lesser degrees of acidosis, the cardinal features of the RTA syndrome become evident. In both groups, the increase in urine pH and the decrease in urinary acid excretion has been attributed largely to increased delivery of filtered bicarbonate to the distal segments of the nephron. In the patients with type 2 RTA, the amount of bicarbonate delivered distally is presumably so unusually large the H^+ secretory process there becomes swamped, intraluminal concentrations of H^+ , and thus titratable acid and ammonium concentrations become minimal, and considerable bicarbonate escapes into the urine.²

In prototypical patients with type 2 RTA, the rate of urinary bicarbonate excretion at normal plasma bicarbonate concentrations is greater than 15 to 20 percent of the rate at which bicarbonate is filtered (Chart 3, Table 1).² This finding permits the inference that the H^+ secretory rate of the proximal nephron is reduced in these patients, since even obliteration of the H^+ secretory process of the distal nephron would presumably not result in urinary loss of more than 10 to 15 percent of the filtered bicarbonate load. A reduced H^+ secretory rate in the proximal tubule

in patients with type 2 RTA accords with the usual concomitance of multiple dysfunctions of the proximal tubule, especially that complex dysfunction referred to as the Fanconi syndrome (generalized aminoaciduria, glucosuria, and increased clearance of phosphate), which is absent in the prototypical patient with type 1 RTA.

Because the fraction of filtered bicarbonate excreted in the urine at normal plasma bicarbonate concentrations is so large in patients with type 2 RTA, the disparity between the rate at which bicarbonate is delivered to the blood by the kidneys and the sum of the rates of bicarbonate filtered and endogenous acid produced is predominantly determined by the magnitude of bicarbonaturia. Accordingly, the rate at which bicarbonate must be administered to maintain plasma bicarbonate concentration normal would predominantly be determined by the magnitude of bicarbonaturia rather than by the concomitant reduction in urinary acid excretion. For example, in a 60 kg patient with a 20 percent reduction of renal bicarbonate reabsorption at a plasma bicarbonate concentration of 25 mmoles per liter, glomerular filtration rate of 50 ml per minute, and urinary acid excretion of 15 mEq per day: (1) the reduction of urinary acid excretion is about $60 - 15 = 45$ mEq per day ($= 0.75$ mEq per kg per day), (2) urinary bicarbonate excretion is about 25 mmoles per liter \times 50 ml per minute \times 0.20 \times 1440 minutes per day $= 360$ mEq per day ($= 6$ mEq per kg per day). Correction of acidosis would theoretically be sustained by the administration of 405 ($= 360 + 45$) mEq of bicarbonate per day (the equivalent of 33 grams of $NaHCO_3$), almost 90 percent of which replaces bicarbonate that the kidney fails to deliver to the blood in conjunction with the titration of filtered bicarbonate. Clearly, for any given fractional bicarbonate excretion rate at normal plasma bicarbonate concentrations, the magnitude of bicarbonaturia, and thus the therapeutic alkali requirement, depends upon the glomerular filtration rate. In some patients, in whom glomerular filtration is normal (or nearly normal), even 20 mmoles of bicarbonate per kg body weight per day fails to sustain correction of acidosis; in others, in whom glomerular filtration rate is decidedly reduced, the amount of correcting alkali may not greatly exceed that required to titrate endogenous non-volatile acids. Thus, the smaller the urinary bicarbonate losses

the more important the reduction in urinary acid excretion becomes as a determinant of the therapeutic alkali requirement.

In some patients with renal tubular acidosis, the physiological characteristics of the renal acidification defect resemble those of both type 1 and type 2 RTA: The pH of the urine remains inappropriately high and slight bicarbonaturia persists even during severe degrees of acidosis, but at normal plasma bicarbonate concentrations the magnitude of bicarbonaturia is sufficiently large to exclude impairment of the H^+ secretory process solely in the distal nephron. The patient whose case history was presented to you this morning exemplifies such a hybrid of types 1 and 2 RTA. In our experience, these patients usually also have the Fanconi syndrome.

Clinical Evaluation of Patients for Renal Tubular Acidosis

A physiological approach to the clinical evaluation of patients with hyperchloremic acidosis is outlined in Table 2. The differential diagnosis of type 1 and type 2 RTA can often be made simply with measurements of urinary pH, serum and urinary CO_2 content, and serum and urinary creatinine concentrations. Urinary CO_2 content and creatinine concentrations required to calculate the percentage of filtered bicarbonate excreted can be obtained on untimed (spot) collections (see Table 2).

Clinical Spectrum of RTA

The clinical spectrum of type 1 RTA is outlined in Table 3. In adult patients, type 1 RTA occurs most often either as a familial renal disease (familial RTA), transmitted as an autosomal dominant trait, or in association with certain autoimmune disorders (autoimmune RTA), especially Sjögren's syndrome. Autoimmune RTA occurs almost exclusively in women. In young women with seemingly idiopathic RTA, the findings of increased serum levels of IgG, of increased hemagglutination titers for rheumatoid factor, or of renal histopathological changes resembling the interstitial nephritis of Sjögren's syndrome, has led to the recognition of an autoimmune disorder. With the exception of amphotericin B nephropathy and renal transplantation, the remaining disorders listed in Table 3 are either relatively uncommon or uncommon causes of RTA. RTA may occur in

TABLE 2.—Clinical Evaluation of Patients for Renal Tubular Acidosis

1. Establish presence of acidemia; hyperchloremia and reduced serum CO_2 content may reflect primary respiratory alkalosis.
 2. Exclude extrarenal causes of hyperchloremic acidosis: administration of ammonium chloride, arginine or lysine hydrochloride; diarrhea or drainage of intestinal, pancreatic, or biliary secretions; injudicious administration intravenously of bicarbonate-free, chloride-containing solutions.
 3. Determine pH (with pH-paper) of each freshly voided urine specimen, for 2 to 3 days before treatment, if prudent:
 - a) If the pH is >5.8 on several specimens, diagnosis of RTA is established;
 - b) If, in addition, the pH is <5.5 on some specimens, diagnosis of type 1 ("distal") RTA is excluded.
 4. Determine pH of each urine specimen during the period of gradual correction of acidosis with alkali therapy; if not already established, the diagnosis of RTA is indicated by values of urine pH >6.0 when arterial plasma $[HCO_3^-] <20$ mM/L (or venous CO_2 content <23 mM/L).
 5. After acidosis has been fully corrected (arterial plasma HCO_3^- 22 to 26 mM/L, venous serum CO_2 content 25 to 30 mM/L) for 2 weeks and the serum $[K^+]$ normalized, measure the concentrations of bicarbonate and creatinine in plasma^(p) and urine^(u) (spot collection) and calculate the percentage of the filtered load of bicarbonate excreted (PBE), $(100 \times [HCO_3^-]_u \times [creat]_p) / ([HCO_3^-]_p \times [creat]_u)$:
 - a) PBE $>15\%$ indicates a 15% reduction in renal bicarbonate reabsorption and establishes the diagnosis of type 2 ("proximal") RTA.
 - b) PBE $>15\%$ in a patient whose urine pH was persistently >6 during severe acidosis ($[HCO_3^-]_p <10$ to 12 mM/L) suggests impairment of acidification processes of the distalmost as well as proximal segments of the nephron (hybrid of types 1 and 2 RTA).
 - c) In patients with type 1 ("distal") RTA, PBE is usually $<5\%$, aminoaciduria and glucosuria are absent, and nephrocalcinosis is common.
- (Urinary CO_2 content can be used to approximate $[HCO_3^-]_u$).

patients with hepatic cirrhosis when the kidney is avidly retaining sodium; it is believed to be a reversible functional disorder associated with reduced sodium delivery to the distal segments of the nephron.

The clinical spectrum of type 2 RTA is outlined in Table 4. Most of the conditions listed give rise to multiple dysfunctions of the renal proximal convoluted tubules. In adult patients without primary renal disease, perhaps the most common disorders likely to cause type 2 RTA are multiple

TABLE 3.—Clinical Spectrum of Type 1 RTA (“classic” RTA, “distal” RTA)

Primary (no obvious systemic disease)
Sporadic
Genetically transmitted
Genetically transmitted systemic diseases
Ehlers-Danlos syndrome
Hereditary elliptocytosis
Fabry's disease
Hereditary fructose intolerance
(after chronic fructose ingestion)
Galactosemia
(after chronic galactose ingestion)
Autoimmune disorders
Sjögren's syndrome
Hyperglobulinemic purpura
Idiopathic hypergammaglobulinemia
Lupoid hepatitis
Disorders causing nephrocalcinosis
Hyperparathyroidism
Hyperthyroidism
Vitamin D intoxication
Primary renal disease
Medullary sponge kidney
Pyelonephritis (?)
Amphotericin B nephropathy
Renal transplantation
Hepatic cirrhosis

myeloma and gastrointestinal disorders in which malabsorption is associated with chronic hypocalcemia and secondary hyperparathyroidism. The occurrence of type 2 RTA in patients with chronic renal insufficiency due to the common forms of chronic progressive renal disease (glomerulonephritis, nephrosclerosis, pyelonephritis, polycystic disease) will be discussed at another time.

Pathogenesis of RTA

The molecular basis of the renal acidification defect in type 1 RTA has not been elucidated in any disease. Because the familial form of the disorder is transmitted as a dominant trait, and because many of the “causes” of the disorder are characterized by extrarenal structural abnormalities (Ehlers-Danlos syndrome, elliptocytosis) or give rise to characteristic structural abnormalities of the renal tubules or interstitium (nephrocalcinosis, immunoglobulin deposition, interstitial nephritis, medullary sponge kidney), it has been suggested that the underlying disturbance of the H^+ secretory process is structural in character rather than metabolic or enzymatic. In the case

TABLE 4.—Clinical Spectrum of Type 2 RTA (“proximal” RTA)

Primary (no obvious systemic disease)
Sporadic; transient (infants)
Genetically transmitted
Genetically transmitted systemic diseases
Cystinosis
Lowe's syndrome
Wilson's disease
Tyrosinosis
Hereditary fructose intolerance
Disorders associated with chronic hypocalcemia and/or secondary hyperparathyroidism
Vitamin D deficiency
Vitamin D dependency
Chronic renal insufficiency
Multiple myeloma
Including light-chain variant,
Idiopathic immunoglobulinuria
Amyloidosis
Nephrotic syndrome
Renal transplantation
Drugs
Acetazoleamide
Sulfanilamide
Outdated tetracycline
Methyl-5-chrome (diacramone)
Heavy metals

of the familial RTA, the distinction between a structural and enzymatic abnormality may not be very meaningful if the abnormality involves a 50 percent reduction in the amount or activity of a cell membrane-bound enzyme critical for H^+ transport.

The possibility that an abnormality of the permeability of the distal nephron to H^+ could underlie the renal acidification defect in type 1 RTA is suggested by the occurrence of apparently typical type 1 RTA in patients with nephropathy caused by amphotericin B, an antifungal antibiotic that can alter cell membrane permeability and apparently increase passive permeability to H^+ in certain H^+ -secreting epithelia. In studies of acidification in the urinary bladder of the turtle, Steinmetz and Lawson⁸ demonstrated an amphotericin-induced acidification defect with physiological characteristics similar to those of type 1 RTA: net H^+ secretion was normal or only slightly reduced when passive electrochemical forces restricting H^+ secretion were minimized (cf. the minimally reduced H^+ secretory rate and HCO_3^- reabsorption rate at normal plasma bicarbonate concentrations in type 1 RTA), but H^+ secretion against a H^+ concentration gradient was

decidedly reduced (cf. the inappropriately high urinary pH and reduced urinary acid excretion during acidosis in type 1 RTA).

Information pertaining to the pathogenesis of type 2 RTA has been provided by studies of renal carbonic anhydrase inhibition, by studies of the reversible proximal tubular dysfunction induced by fructose administration in patients with hereditary fructose intolerance, and by studies of the role of hyperparathyroidism in clinical type 2 RTA. Because inhibition of renal carbonic anhydrase induces a renal acidification defect physiologically indistinguishable from that of prototypical type 2 RTA, the possibility must be recognized that in some of the clinical or experimental causes of type 2 RTA the impairment of renal H^+ secretion is mediated via inhibition of renal carbonic anhydrase activity. The metabolic correlates and physiological character of the fructose-induced proximal tubular dysfunction in patients with hereditary fructose intolerance has been delineated by Dr. R. Curtis Morris, Jr. and his associates.^{9,10}

A renal acidification defect like that of type 2 RTA can also be induced experimentally in normal subjects by acute administration of parathyroid hormone.¹¹ Because many patients with type 2 RTA are chronically hypocalcemic, this observation raises the possibility that the impairment of renal H^+ secretion in type 2 RTA is in part due to increased circulating levels of parathyroid hormone. This possibility has been supported by the finding that serum concentrations of parathyroid hormone are increased in hypocalcemic patients with type 2 RTA,¹² and that maneuvers that suppress parathyroid hormone secretion are attended by a striking amelioration of the renal acidification defect.^{12,13}

Renal Excretion of Potassium and Sodium in RTA

Renal potassium and sodium wasting, and secondary hyperaldosteronism, are common complications in both types 1 and 2 RTA. In patients with type 1 RTA, these abnormalities have generally been regarded as indirect consequences of the renal acidification defect, and not the consequence of independent abnormalities in renal potassium (K^+) and sodium (Na^+) transport. This belief is based on the observation that correction of acidosis with alkali therapy in patients

with type 1 RTA predictably results in a reduction in the urinary excretion rates of potassium, sodium, and aldosterone; with sustained correction of acidosis, potassium and sodium balance may become sufficiently positive to correct hypokalemia and hyperaldosteronism.¹⁴ Most patients with type 1 RTA do not require potassium supplements to maintain normokalemia when correction of their acidosis is sustained.

According to the conventional formulation of the pathogenetic mechanisms, renal sodium and potassium wasting in type 1 RTA is a consequence of the reduction in net rate of renal H^+-Na^+ exchange in the distal nephron imposed by the limitation there on attainable cell-to-lumen H^+ concentration gradients. The reduction in renal H^+-Na^+ exchange, in addition to diminishing sodium reabsorption, results in a "reciprocal" increase in renal K^+-Na^+ exchange and thus causes renal potassium wasting. The "reciprocal" increase in renal K^+-Na^+ exchange has been predicted from the hypothesis that H^+ and K^+ compete for a common secretory pathway in the distal nephron, and would be expected to occur when sodium depletion stimulates aldosterone secretion. With correction of acidosis, the attendant increase in intraluminal bicarbonate concentration and pH (reflected by the increased urinary pH) is presumed to remove the gradient restriction on renal H^+-Na^+ exchange. As a consequence, the urinary excretion rate of sodium decreases, the stimulus for aldosterone secretion is diminished, K^+-Na^+ exchange decreases, and the urinary excretion rate of potassium decreases.

But the finding in patients with type 1 RTA that urinary sodium and potassium excretion decrease when acidosis is corrected does not necessarily mean that impaired renal conservation of these cations is entirely due to some consequence of the presumed defect in distal H^+ gradient-generating ability. In many patients, a persisting impairment of renal sodium conservation can be demonstrated during dietary sodium restriction and sustained correction of systemic acidosis by oral potassium bicarbonate administration, even though the urinary pH is high enough to indicate removal of the abnormal gradient restriction on H^+ secretion.¹⁵ Moreover, in some patients, renal potassium wasting persists, in association with persisting hyperaldosteronism, despite sustained correction of acidosis with alkali therapy.¹⁶ Whether such impairments

of renal sodium and potassium transport are interrelated, and to what extent they reflect primary abnormalities of renal sodium and potassium transport or secondary functional or structural abnormalities of the kidney, remains to be determined.

In patients with type 2 RTA, the occurrence of renal sodium and potassium wasting would not be surprising, since most patients have generalized impairment of proximal tubular function. If proximal sodium and chloride reabsorption is as severely impaired as other proximal tubular functions, salt wasting is likely to be severe. Systematic studies of renal sodium conservation have not been performed in patients with type 2 RTA. In our experience, in studies performed with Dr. Edward Biglieri at San Francisco General Hospital, aldosterone secretion and excretion remain increased in these patients, despite sustained correction of acidosis, and despite the provision of normal or supernormal amounts of dietary sodium.

In contrast to patients with type 1 RTA, in patients with type 2 RTA, renal potassium wasting frequently becomes more severe when acidosis is corrected with alkali therapy, and usually persists when correction of acidosis is sustained.¹⁷ These findings can be attributed in part to excessive sodium and bicarbonate delivery to the distal nephron. Because sodium bicarbonate reabsorption in the proximal nephron is impaired in these patients, raising the plasma bicarbonate concentration to normal levels floods the distal nephron with sodium and bicarbonate. In the presence of hyperaldosteronism, delivery to the distal nephron of such supernormal amounts of sodium with the relative impermeant bicarbonate anion would be expected to increase intraluminal negativity, augment net potassium secretion in the distal nephron, and thereby promote renal potassium wasting. At normal plasma bicarbonate concentrations, the fraction of the filtered load of potassium excreted frequently exceeds 1.0, which indicates net renal secretion of potassium. The degree of

renal potassium wasting in these patients varies directly with the magnitude of bicarbonaturia.

Many important clinical problems related to renal tubular acidosis (nephrolithiasis and nephrocalcinosis, pyelonephritis, osteodystrophy, nephrogenic diabetes insipidus, the Fanconi syndrome), as well as the pathophysiology of variants of renal tubular acidosis observed in infancy, in patients with mineralocorticoid deficiency, and in patients with chronic renal failure, will not be discussed. These topics are covered in the publications listed in the references.

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Important Advances in Clinical Medicine

Epitomes of Progress -- Pathology

The Scientific Board of the California Medical Association presents the following inventory of items of progress in Pathology. Each item, in the judgment of a panel of knowledgeable physicians, has recently become reasonably firmly established, both as to scientific fact and important clinical significance. The items are presented in simple epitome and an authoritative reference, both to the item itself and to the subject as a whole is generally given for those who may be unfamiliar with a particular item. The purpose is to assist the busy practitioner, student, research worker or scholar to stay abreast of these items of progress in Pathology which have recently achieved a substantial degree of authoritative acceptance, whether in his own field of special interest or another.

The items of progress listed below were selected by the Advisory Panel to the Section on Pathology of the California Medical Association and the summaries were prepared under its direction.

Reprint requests to: Division of Scientific and Educational Activities, 693 Sutter Street, San Francisco, Ca. 94102

Small Intestinal Biopsies

Since the advent of Ian Wood's studies on biopsy material obtained from the gastric mucosa by peroral suction, diagnosis of small intestinal mucosal disease has become possible

with improved instrumentation. Currently, the suction biopsy tubes with multiple apertures and new hydraulic models used for this purpose quickly and safely obtain tissue which is suitable for study.

The normal histological characteristics of the jejunum are now well described and it is clear that a number of diseases can be diagnosed by characteristic morphologic changes. Fresh specimens must be properly sectioned and mounted, however, before definitive conclusions regarding disease may be made.

The following diseases have characteristic features and may be diagnosed by this method:

1. *Celiac Disease*, childhood and adult, which reveals a flat mucosa without villi, damaged surface epithelium and a variable increase in plasma cells and lymphocytes in the lamina propria. (It is not specific for this entity, since the same lesion may be noted in a patchy fashion in patients with radiation enteritis, dermatitis herpetiformis, after treatment with MER-29 and in some instances of dysglobulinemia.)

2. *Whipple's disease*, due to an organism invading the mucosa, reveals a dense infiltration of the lamina propria with macrophages laden with glycoprotein material, giving the appearance of "foamy cells." Histological diagnosis may be confirmed by positive staining with PAS.

3. *A-beta-lipoproteinemia*, an hereditary disorder, revealed by vacuolated epithelial cells in the upper third of the villi which are stuffed with triglyceride.

4. *Agammaglobulinemia*, characterized by the absence of plasma cells in the lamina propria. The mucosa may be flat or have a normal villous architecture.

5. *Parasitic disease*. Specifically, giardia lamblia may be found attached to the surface of the villous or located in the intervillous spaces. Various forms of coccidia (*Isospora belli*) may be found in epithelial cells.

Nonspecific findings which may be present in a number of disease entities include clubbing of the villi, eosinophilic infiltration, and lacteal dilatation, the latter being characteristic of diseases in which the lymphatic channels are obstructed.

Rarely, lymphoma mastocytosis, amyloidosis, and granulomous disease such as regional enteritis may be diagnosed in random specimens.

MARVIN SLEISINGER, M.D.

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Role of Properdin in Kidney Diseases

The properdin system, first described by Pillemer and coworkers, was shown to combine with zymosan with inactivation of the third component of complement without significant inactivation of the earlier components of complement. However, there has been some controversy over the exact biological role of properdin.

Recently, Gewurz et al demonstrated that serum levels of properdin were uniformly decreased in patients with acute glomerulonephritis and in about half of patients with chronic membranoproliferative glomerulonephritis with hypocomplementemia. Westberg et al performed immunofluorescent studies on various immunologic kidney diseases with antiserum to purified properdin. All patients with acute post-streptococcal glomerulonephritis and chronic membranoproliferative glomerulonephritis had deposition of properdin and C3 in the glomeruli often without immunoglobulins. The deposition of properdin and C3 was seen as "humps" or in a lobular pattern on the basement membrane of the glomeruli.

Activation of C3 by the properdin system without antibody may explain normal levels of the earlier components of complement in the serum and the deposition of C3 often without immunoglobulins in kidneys of patients with acute glomerulonephritis or chronic membranoproliferative glomerulonephritis.

ROBERT M. NAKAMURA, M.D.

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Significance of Mitochondrial Antibody Test

The mitochondrial antibody found in serum of human patients can be demonstrated by an indirect immunofluorescent test, currently used in clinical laboratories.

The antibody is found in 94 percent of patients with primary biliary cirrhosis, often in very high titers and in 25 to 30 percent of patients with active chronic hepatitis and cryptogenic cirrhosis. The level of antimitochondrial antibody in the serum in primary biliary cirrhosis may vary from trace amounts to titers of 1:6000 and does not correlate with the severity or duration of the disease.

The test is helpful in differentiation of surgical and non-surgical cases of obstructive jaundice since mitochondrial antibody is usually absent in jaundiced patients with extra-hepatic obstructions, drug sensitivity or viral hepatitis. In patients developing jaundice due to chlorpromazine and halothane sensitivity, a low titer of mitochondrial antibody may be seen and disappear upon recovery. The antibody is usually absent in alcoholic cirrhosis.

Mitochondrial antibody of low titer was found in 51 percent of patients showing chronic false positive reactions for syphilis in the absence of detectable liver abnormalities. It is likely that the association of chronic false positive reactions for syphilis and the presence of mitochondrial antibody is associated in a select group of patients with a particular sort of collagen or autoimmune disease.

ROBERT M. NAKAMURA, M.D.

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Significance of Smooth Muscle Antibodies in Liver Disease

Smooth muscle antibody can be detected in serum samples in the clinical laboratory. This antibody is found mainly in active chronic hepatitis, primary biliary cirrhosis, cryptogenic cir-

rhosis and present in less than 2 percent of normal subjects. The smooth muscle antibody test is helpful in differentiating active chronic hepatitis from systemic lupus erythematosus (SLE) as smooth muscle antibody is not usually seen in SLE, whereas a positive LE cell test may be observed in both SLE and active chronic hepatitis. The role of smooth muscle antibody in the pathogenesis of chronic liver disease is unknown.

Recently, smooth muscle antibody has been found in cases of acute viral hepatitis. Highest titers were observed during the first month after onset of symptoms. The smooth muscle antibody is most likely related to liver cell damage. No definite correlation between the antibody and hepatitis associated antigen was noted.

Serum IgG and IgM anti smooth muscle antibodies have been reported in 21 percent of patients with intrinsic asthma contrasted with a much lower incidence in extrinsic asthma and chronic bronchitis. The pattern of immunofluorescence observed in cases from intrinsic asthma is distinct from that commonly seen in patients with liver disease.

ROBERT M. NAKAMURA, M.D.

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Molecular Basis for a Simple, Specific Test for S Hemoglobin: The Murayama Test And Desickling of Sick Cells with Urea

The Murayama test, a new specific test for S hemoglobin, is based on the molecular mechanism of sickling for S hemoglobin proposed by Murayama. The test depends on a feature of molecular structure: hydrophobic bonds formed between interacting tetramers by the No. 6 valine, which is substituted for glutamic acid near the N-terminal end of each β S globin chain. Ex-

istence of these particular hydrophobic bonds is manifested in deoxygenated, concentrated hemolysates by reversible sol-gel transformations at 0° and 37°C. Deoxygenated hemolysates of S hemoglobin gel at 37°C and liquefy at 0°C. In such systems, demonstration of reversible, temperature-dependent sol-gel transformations (a negative temperature coefficient of gelation is specific for S hemoglobin or the S structural variant, hemoglobin C (Harlem). The test is simple, has clear end-points, will detect both homozygous and heterozygous S hemoglobin, and is specific.

The molecular mechanism for sickling of hemoglobin S has been so precisely defined by the Murayama hypothesis that by extension we have selected on theoretical grounds urea as a chemical desickling agent. Urea attacks intertetrameric hydrophobic bonds implicated by Murayama to break those specific pathogenetic bonds formed in part by the substituted valine residues. Urea forms new hydrophobic bonds of its own with the improperly structured hemoglobin S tetramer, altering the steric structure of the hemoglobin S molecule WITHOUT adversely affecting the vital function of oxygen transport. Thus, by chemical manipulation, a lethal molecular property is inhibited by steric hindrance with the formation of urea-hemoglobin complex, since tetrameric polymerization or "stacking," that is, sickling, is impossible.

PAUL L. WOLF, M.D.

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- Nalbandian RM, Henry RL, Shultz G, et al: Sick Cell Crisis Terminated by Use of Urea in Invert Sugar in Two Cases. Fort Knox, Kentucky, U S Army Medical Research Laboratory Report No 896, September 17, 1970

Value of Histochemistry in the Investigation of Human Muscle Diseases

Awareness of the value of histochemical techniques in the investigation of human neuromuscular disorders has increased in the last few years. Such studies have allowed the definition

of two or more fiber types, recognition of abnormalities in the reactivity and localization of biochemically defined organelles, determination of the magnitude of collateral reinnervation from type-specific fiber grouping and precise identification of regenerative activity and inflammation.

With such procedures, significant advances have been made in our understanding of the identification and pathogenesis of unusual muscle disorders including nemaline, central core, myotubular and vacuolar myopathy. Increased use of morphometric analysis of fiber types has proved of prognostic and therapeutic value. Newer approaches have placed emphasis on the recognition of the differential susceptibility of fiber types to degeneration or atrophy in a variety of neurogenic and myopathic disorders. Further advances in the recognition and investigation of myopathies will require the continued association of clinician and pathologist.

M. ANTHONY VERITY, M.D.

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Prenatal Diagnosis of Inherited Diseases

A specimen of amniotic fluid (about 10 ml) taken between the 14th and 16th week of pregnancy contains viable cells of fetal origin. The sex of the fetus, chromosomal abnormalities and certain enzyme defects can be diagnosed from these cells after two to four weeks in cell culture. The combined maternal and fetal risk of amniocentesis (probably less than 1 percent) is substantially less than the risk of giving birth to an affected child in families at risk for a detectable genetic disorder (25 percent) or in pregnancies occurring in women over 40 years of age (3 percent). The procedure is not universally applicable, however; not all genetic diseases, and none of the dominant or polygenically inherited disorders, can be detected. The

overall success rate is about 75 percent even under optimal conditions of cell culture and analysis. Physicians must bear in mind that diagnostic amniocentesis should be undertaken with the understanding that abortion is the only available therapy.

JEAN-JACQUES CASSIMAN, M.D.

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Status of C Type Virus in Cat Tumors

C type RNA tumor viruses are proved to be the causative agents of malignant lymphoma and sarcoma in domestic cats. The incidence of feline lymphoma is four to five times greater in cats than in humans. There is no convincing evidence for infectious spread of these agents under natural conditions between cats or from cats to other animals or to man. Evidence suggests but does not prove that the C type virus genome is inheritable, presumably in the form of DNA.

House cats differ from other randomly bred vertebrate species in showing a marked degree of spontaneous expression of their latent C type virus genome in the form of group-specific antigen and replicating C type particles.

A human sarcoma cell line, previously free of C type virus particles, started to produce large numbers of such virus particles after transplantation into a fetal kitten. This virus (RD-114) proved to be no known cat or other mammalian C type virus and may thus be wholly or partially of human origin.

MURRAY B. GARDNER, M.D.

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Evaluation of Hepatotoxicity by Electron Microscopy

Examination of liver biopsy material with the electron microscope can be a useful aid in studying the potential hepatotoxicity of drugs and environmental toxins. Light microscopy frequently reveals only minimal fatty changes, not necessarily indicative of liver abnormality. Ultrastructural studies, however, often disclose proliferation of the smooth endoplasmic reticulum as well as mitochondrial enlargement; also, crystalline inclusions may be found within the mitochondrial matrix. Other alterations include the development of autophagosomes, pigment inclusions, and, with some compounds, increased numbers of microbodies. Proliferation of the smooth endoplasmic reticulum is associated with increased activity of some of the enzymes located in the microsomal fraction.

Although all of these changes have been found in apparently healthy persons, their presence should alert the physician to the possibility of hepatic injury.

Recent studies on the hepatotoxicity of methotrexate indicate that abnormalities may persist for months or even years after the hepatotoxin is withdrawn.

JOHN C. LEE, M.D.

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Lymphomatoid Granulomatosis

Lymphomatoid granulomatosis is a lymphoproliferative disorder associated with angitis and granulomatosis of the lung, resembling and possibly related to Wegener's granulomatosis. The pulmonary lesions are usually multiple, bilateral

and nodular. They resemble metastatic lesions and predominate in the peripheral portions of the lower lobes, chiefly in young males. Frequently there is an accompanying cutaneous angiitis and panniculitis. Nodular renal lesions resembling those in the lungs can occur, but there is not the glomerulonephritis of the Wegener triad. The central nervous system is involved in one-fifth of the fatal cases. The condition occasionally terminates in atypical lymphoma. Pulmonary lesions may be asymptomatic or associated with fever and non-productive cough. Treatment with steroids may be associated with remission or arrest of the process, but this outcome can occur spontaneously.

AVERILL A. LIEBOW, M.D.

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Pulmonary Veno-Obstructive Disease

Intrapulmonary veins can be specifically occluded by thrombosis and organization. The first manifestation may resemble influenza, but more commonly the onset is insidious, with increasing dyspnea as the chief complaint. One-third of the patients are less than 16 years of age. There is progressive right-sided heart failure without evidence of left atrial enlargement. Radiographically wandering pulmonary infiltrates are seen and Kerley lines are prominent. Angiography may reveal focally delayed emptying of pulmonary arteries. Pulmonary wedge pressure may be elevated or normal. The cause is unknown and no method of treatment is available.

AVERILL A. LIEBOW, M.D.

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Microangiopathic Hemolytic Anemia

The sequential activation of the coagulation factors terminating in the production of thrombin and the formation of a fibrin clot normally occurs in the interstices of a platelet plug. On occasion, due to disease, the activation of the procoagulant enzymes occurs widely in the bloodstream and disseminated intravascular coagulation (DIC) results. Whereas DIC is always a secondary mechanism of disease, microangiopathic hemolytic anemia (MAHA) is tertiary. It results from DIC of a certain type and duration.

Schistocytes, red cell fragments of characteristic morphologic pattern, are the hallmark of MAHA. Fibrin microclots produced by DIC are filtered out of the circulation in arterioles, primarily those of lung and kidney. Rapidly moving red cells are sheared by these fine fibrin strands the way cheese can be cut by a taut wire. The resulting damage decreases the ratio of membrane to hemoglobin and hence the deformability of the schistocytes. The most severely damaged cells lyse, releasing hemoglobin. Less severely traumatized cells circulate briefly and are removed within a few hours by the spleen. Only those cells which still possess a high enough ratio of membrane to hemoglobin are deformable enough to persist in the circulation as schistocytes.

In addition to the obvious sequel of anemia, MAHA causes hemoglobinemia as a result of intravascular lysis of severely damaged cells; bilirubinemia due to increased splenic destruction; thrombocytopenia due to DIC; and, should the process become subacute, erythroblastemia as the bone marrow releases nucleated red cells into the peripheral circulation in an attempt to compensate for hemolysis.

Postmortem tissues of patients who had MAHA during life often do not show the microclots of fine fibrin strands that cause the red cell damage, for they are rapidly incorporated into coarser, more amorphous deposits of fibrin. Strongly

stained by fibrin stains, these semilunar deposits are highly characteristic of postmortem kidney sections and form the "microangiopathy" of MAHA. Studies of the correlation between the degree of microangiopathy and the severity of schistocytosis opened the way to the present understanding of the pathophysiologic features of this syndrome.

In animal experiments the entire process can be simulated by injection of a procoagulant enzyme such as arvin after first blocking the fibrinolytic system with epsilon amino caproic acid. The fragmentation of red cells by fibrin strands has also been studied and photographed *in vitro*.

The clinical picture is that of a hemolytic process superimposed upon the pathophysiology of the DIC and complicated yet further by changes resulting from the primary disease process. As a result treatment of MAHA is properly directed first at the underlying disease and secondarily at the DIC.

Those diseases most frequently involved are obstetrical disorders (abruptio placenta, retained dead fetus), the hemolytic uremic syndrome, malignant hypertension, polyarteritis nodosa, Gram-negative sepsis, and disseminated adenocarcinoma.

MAHA has considerable clinical relevance for it is easily recognized by examining a properly prepared blood film. When the typical schistocytes are present along with thrombocytopenia, DIC can be confidently diagnosed.

BRIAN S. BULL, M.D.

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- McKay DG: Progress in disseminated intravascular coagulation. *Calif Med* 111:186-199, Sep 279-289, Oct 1969

Platelet Transfusions

Platelet transfusion therapy has progressed on the basis of new data in human immunogenetics and new technical advances yielding greatly increased availability of platelet concentrates (PC). The essential indication for platelet transfusions

is still thrombocytopenic hemorrhage, and a careful hematological evaluation continues to be necessary to rule out complications, such as coagulopathy or disseminated intravascular coagulation, for which platelet transfusions could be ineffective or even contraindicated. The risks of transmission of hepatitis or cytomegalovirus are the same as for other blood components, and once platelet transfusion support is decided upon, platelet concentrates are the preparation of choice.

Each unit of PC produces, at about four hours post-transfusion in an adult, an increment in the recipient's platelet count of about 12,000 per cu mm. An adult with no autologous platelet production would thus require approximately four units of PC twice weekly to maintain a platelet count greater than 20,000 per cu mm. If hemorrhage occurs with platelet counts above that level, then another defect in hemostasis must be sought. Fever, sepsis, hepatosplenomegaly, and antiplatelet allo-immunity or auto-antibodies will all decrease platelet transfusion effectiveness; splenectomy will increase effectiveness; and androgens and prednisone (up to 100 mg a day) will not alter effectiveness. Currently, there are no clinically practical crossmatching tests for platelets. Rh differences have no effect, and ABO differences have a variable effect on recovery of transfused platelets. Whenever possible, rules of compatibility (for example, O→A, but not A→O) should be followed, but in an emergency, incompatibilities may be breached with little risk to the recipient (Note: This holds for PC only). For any multi-transfused patient population the clinically most significant antigens are those of the HL-A system. Multi-transfused patients become refractory to transfused platelets because of allo-immunity to foreign HL-A antigens at a median of about eight weeks. HL-A compatible platelets, however, can be tolerated indefinitely with no evidence of allo-immunization and no loss of transfusion efficacy. Utilizing known immunogenetic data for the HL-A system, each sibling of a patient will have a one-in-four chance of being HL-A compatible, compared with a one-in-fifteen-hundred chance for unrelated donors. In fact, bi-weekly four-unit plateletpheresis of a sibling donor has kept aplastic anemia or leukemia patients free of bleeding for periods as long as three years, and in several instances these compatible platelets had to be flown hundreds of

miles from donor to recipient each time. Patients who have a significant post-transfusion increment clearly benefit from platelet transfusions. There are, however, conflicting opinions and little evidence concerning the value of platelet transfusions in patients with ITP or allo-immunization sufficient to block any post-transfusion rise in platelet count. Nevertheless, in the presence of significant bleeding in either of those two problem cases, most hematologists would probably attempt a trial of platelet transfusions. Although compatible platelets could stop the bleeding in the allo-immune patient, to date there have been no platelet donors known to be compatible with ITP antiplatelet factors. Finally, the rules of immunogenetics have also been applied to iso-immune neonatal thrombocytopenic purpura, with plateletpheresis of the mother providing an excellent source of compatible platelets to protect the infant until his own platelets have recovered from the insult of the transplacentally acquired maternal antiplatelet antibodies.

F. C. GRUMET, M.D.

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Platelet Storage

Recent advances in techniques of processing platelets for transfusion have extended the blood bank storage life of this valuable blood product from approximately six hours to almost 72 hours. The significance of this prolongation of shelf life is that blood banks are now capable of providing platelet units at any time, day or night, without having to call in new donors. Blood collected during regular donor hours is drawn into a closed system of several interconnecting bags made of new plastics with ACD or CPD anticoagulant. Because platelets are sensitive to low temperatures, the freshly drawn unit of whole blood must be immediately centrifuged at room temperature (22°C). The packed red cells, after separation from the platelet-rich plasma (PRP), can then be kept at the standard 4°C blood storage temperature. (Logistically, the two-temperature require-

ment means that blood drawn in bloodmobiles and kept refrigerated in transit back to the processing center is far less suitable for extraction of platelets than is blood drawn at the center itself.) The PRP can be further centrifuged, again at 22°C, to provide a platelet concentrate (PC) with approximately 75 percent of the platelets of the original 500 ml of blood now in a volume of 15 to 50 ml. With no further additives or manipulations, the PC is stored at room temperature, with gentle agitation. The PC is then immediately available when needed for transfusion. The advantage of ready availability greatly outweighs the small loss of effectiveness incurred during the first three days of room temperature storage of PC. Techniques for more prolonged storage of platelets, either by freezing or by use of new additives, are currently under investigation in a number of laboratories.

F. C. GRUMET, M.D.

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Reed-Sternberg Cells in Non-Hodgkin's Disease

Reed-Sternberg cells (RSC) are not pathognomonic for Hodgkin's disease, but the diagnosis of Hodgkin's disease is not made in their absence. Recent reports confirm a previous, but seldom emphasized, observation that Reed-Sternberg cells mean Hodgkin's disease only when they are in association with the proper histopathologic background features, or milieu, of one of the sub-types of Hodgkin's disease.

Multinucleated cells resembling Reed-Sternberg cells have been described in a variety of reactive and neoplastic proliferations. A striking example is the presence of multinucleated cells, which may be indistinguishable from the diagnostic cells of Hodgkin's disease, in lymphoid tissue from persons with infectious mononucleosis. The cellular proliferation in tissue in infectious mononucleosis is predominantly that of an extraordinary number of plasma cell precursors

or immunoblasts, and cytoplasmic lymphocytes, unlike the milieu of Hodgkin's disease. The immunoblasts in infectious mononucleosis may present in a variety of bizarre forms, with some cells closely resembling or approaching the criteria for diagnostic Reed-Sternberg cells. A diagnosis rests not on the presence of Reed-Sternberg cells

alone, but on their presence within a particular histopathological setting.

BARBARA H. TINDLE, M.D.

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University of California, Davis

CORRECTION

An error in wording was made in the "Epitome" item "Intestinal Bypass for Morbid Obesity" which appeared on page 66 of the March 1972 issue. To correct it, the sentence reading, "The open distal jejunum is drained by anastomosis with the transverse colon while the proximal jejunum is closed," should be changed to "The open proximal ileum is drained by anastomosis with the transverse colon while the distal jejunum is closed."

Multiple Sclerosis: An Unsolved Problem

THE PUZZLE OF MULTIPLE SCLEROSIS has attracted the attention of investigators in the field of neurology for many years. Etiological theories have been offered in plethora in the past, and even in the last twenty years widely different causes have been suggested, including spirochetal infection,^{1,2} non-immune lipolytic agents,³ and vascular disturbance secondary to increased platelet stickiness.⁴ None of these theories is given serious credence at present, but their sheer diversity reflects the continuing uncertainty about the roots of the disorder.

Although the cause of multiple sclerosis is still unknown, the view most favored currently is that the disease is immunologically mediated and further that a remote early-life exposure, perhaps a viral infection, may be the original event. Most of the evidence to support this notion comes from two lines of research: (1) epidemiological studies, and (2) investigations of experimental allergic encephalomyelitis (EAE) in animals. The epidemiological evidence is at best indirect, and the validity of the findings in EAE depends upon how faithfully EAE represents a model of multiple sclerosis, a point which deserves further comment. Elsewhere in this issue of CALIFORNIA MEDICINE, Seil has set forth in satisfying detail the experimental evidence, particularly that gained from the study of EAE, which has served to shape current opinion.

EAE is an acute monophasic illness from which the animal either dies or recovers completely. Neither clinically nor pathologically does EAE resemble chronic multiple sclerosis, and a chronic fluctuating form of EAE analogous to multiple sclerosis has not been produced experimentally.

Why, then, has EAE been studied so extensively? The major reasons are, as summarized by Alvord,⁵ (1) the finding of serum antibodies in both EAE and active multiple sclerosis which will demyelinate central nervous system tissue cultures, (2) the close resemblance pathologically of multiple sclerosis to the cerebral form of rabies post vaccinal encephalomyelitis, which is considered to be human EAE, and (3) the remarkably similar susceptibility, according to age group, to multiple sclerosis and to rabies post-vaccinal encephalomyelitis. These observations form the link between multiple sclerosis and EAE.

Claims of successful treatments for multiple sclerosis have been even more variegated and fanciful than theories as to its cause. Partly this is due to the variable and remittent nature of the illness, which on occasion permits any therapeutic measure to appear effective. In view of the intense research interest in the immunological aspects of multiple sclerosis, one would expect that immuno-suppressive agents other than corticosteroids and ACTH are under investigation. To date, only a few uncontrolled pilot studies have been reported, and no large-scale, controlled program has been undertaken. At present the only generally accepted method of therapy is short-term, high dosage adrenocorticotrophic hormone for recent worsening of the disease.⁶ There is an equally good rationale for using dexamethasone instead of ACTH, but so far only ACTH has been subjected to a large systematic study.

ARTHUR K. ASBURY, M.D.

*Department of Neurology
University of California San Francisco, and
San Francisco Veterans Administration Hospital*

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Who Is To Decide and Who Is To Pay?

A PHILADELPHIA COURT RECENTLY ordered a physician to pay the hospital bill of a patient deemed by the judge to have been hospitalized unnecessarily. The case is being appealed and the appeal is being aided by the American Medical Association in behalf of all physicians, as indeed it should be. But whatever the outcome, once again serious questions are raised with respect to who is responsible for what in patient care, how is the decision to be made to do what, and who is to pay the bills. At present physicians are expected to make the principal decisions in collaboration with patient and family. These decisions generally involve expenditure of money by others who took no part in making the decision but who nevertheless have responsibility for the wise and proper expenditure of funds which they control. Such being the case, they may challenge the decision after the fact, and since they control the funds, even refuse to pay if they do not consider the costs to be justified. It was just this which gave rise to the court case cited above.

The crucial event occurred when it became both desirable and necessary to spread the growing risk of medical care costs beyond just the patient and his family. As soon as this was done the parties who pay the bills had a legitimate interest in what costs were incurred and how they were incurred. With government involvement in financing care for various segments of the population, a new and powerful force was added. Government then had a legitimate interest beyond simply protecting the consumer. Government is supposed to see that public funds are wisely and appropriately used, and government possesses the ultimate power of compulsion to

see that this is accomplished. Thus what was once a private affair between a doctor, his patient and the family is now quite evidently of fairly wide general and even public interest.

The physician and his patient are both in key positions, the physician because his professional judgment profoundly influences the costs to be incurred, and the patient because it is his individual needs which require the services though they may be paid for by others. In this age of consumerism the simplistic approach is to hold the physician responsible for what medical care costs are incurred and to bring his actions under control in thoughtless disregard of any short or long-range effect this approach may have upon the quality or quantity of the care received by the patient. This appears to be the approach espoused by the Philadelphia judge.

If physicians are to be held responsible—and also liable—for medical care costs incurred by their patients, it is only natural that they try to reduce the extent of their liability. How can they do this? The evidence to date suggests that it would be foolish for physicians to rely upon the professional competence of judges, the courts and other third parties with respect to what is appropriate in patient care. The professional liability record to date speaks eloquently on this point. But there are other possibilities. Physicians could see fewer and more carefully selected patients and thus reduce their liability. They could do less for their patients. To do more would increase their potential liability. They could do nothing at all without getting prior authorization from the payor, thus involving the payor in the decision to render each service. In many situations this could actually be a practical answer but certainly not in all. They could try to get insurance to cover any liability they might incur. This seems quite impractical. Or they could form a tough union to protect themselves. This has been suggested and is right now being discussed quite widely. But any of these steps would further erode something very important in patient care—that is, the physician's right and responsibility to do what he believes best for the patient and the patient's confidence in both the physician's ability and willingness to do just this.

What, then, is to be done? It must be granted that spreading the financial risk legitimately involves third parties in responsibility for costs in patient care, but this should not be allowed to

interfere with the care of a patient who is sick or injured. In these circumstances, who is to make the judgment of what is to be done? The patient, the physician, and various third parties each has much at stake. Retrospective judgments are likely to be arbitrary and usually unfair to someone. Prospective judgments may be equally arbitrary and unfair, and themselves costly and time consuming if everyone is consulted who might be. It would appear that the best and most economic medical care rests upon the good judgment of those involved at the time and place the care is given. It therefore follows that if improvements are to be made the emphasis should be upon improving judgment, and not upon punishment or professional liability or close governmental regulation of individual circumstances which by their nature defy standardization. It would appear then that the primary focus should be upon peer review of what actually takes place and upon the continuing education of all concerned. It may be necessary to take steps to ensure that all who are properly concerned, and not just physicians, become more involved in both these processes. Peer review and continuing education have been and continue to be among the primary goals of the California Medical Association. The CMA is an acknowledged leader in both these activities, which must now be further developed and expanded until they are acknowledged to meet the need. Absent a fair, effective, comprehensive peer review system, someone will fill the void, and it does not take much imagination to guess who it will be.

—MSMW

Mycoplasmas

MYCOPLASMAS ARE THE smallest living things able to grow outside of cells. Elsewhere in this issue of CALIFORNIA MEDICINE, Harwick, Kalmanson and Guze have reviewed the pathogenic poten-

tialities of these organisms for man. In this respect some mycoplasmas occupy a position analogous to the staphylococcus in that many people are carriers but few become infected while *Mycoplasma pneumoniae* is more analogous in pathogenicity to the pneumococcus or *Streptococcus hemolyticus*. Each species of virulent mycoplasma has strict tissue tropism and host specificity and in this they more closely resemble viruses. Because several saprophytic mycoplasmas are commonly found in man, diagnostic significance of an isolate is not established until the organism is identified by serology or other suitable tests.

The incidence of pneumonia caused by *Mycoplasma pneumoniae* has now been estimated in several parts of the world. The disease tends to occur in sporadic outbreaks without seasonal pattern. At the peak of such outbreaks the prevalence seldom equals or exceeds that of an epidemic of influenza type A or B. As with the viral respiratory infections, *M. pneumoniae* is responsible for a considerable amount of febrile illness, without pneumonia, which closely resembles the milder forms of influenza.

Apparently *M. pneumoniae* spreads less readily than influenza virus but crowded living conditions can greatly increase the rate of infection. As pointed out by Harwick, Kalmanson and Guze in their current review, atypical pneumonia was an important problem during World War II and sometimes still is in Army training centers. In the civilian population, outbreaks confined to a school or a family are common. A formalin-killed *M. pneumoniae* vaccine is available but its effectiveness is marginal and there is some doubt as to whether it is necessary for the civilian population in general. Mortality from *M. pneumoniae* infection is now very low. However, given a return of the conditions seen in 1940-45, the need for an effective vaccine might become urgent.

When grown on artificial medium for a hundred or more serial passages, *M. pneumoniae* becomes attenuated for man and experimental animals. But such attenuated strains when sprayed into the respiratory tract of volunteers still cause illness in some individuals. Chanock and his associates have developed temperature sensitive mutants of *M. pneumoniae* which, in experimental animals, infect the respiratory tract but grow

less readily at 37°C than at 32°C and seldom produce pneumonia.¹ Temperature-sensitive mutants of viruses such as influenza and respiratory syncytial have also been obtained for possible use in vaccination by the respiratory route. Current concepts point to this route of immunization for control of respiratory disease because some local stimulation of lymphocyte mediated immunity may occur and production of IgA secretory antibodies is said to be favored. The safety factor remains to be investigated more thoroughly. Also under investigation is the possibility of using antigens isolated from *M. pneumoniae* for immunization as has been done with the specific polysaccharide antigens of pneumococci.

The use of relatively ineffective formalized vaccines is not free of hazards. Not unlike the experience with inactivated measles vaccine was the finding of at least one group of investigators that the incidence and severity of illness among those without detectable antibodies following *M. pneumoniae* vaccine was greater than in the controls.² A possible explanation for this paradox is that no antibodies were present on the surface of the respiratory epithelium to prevent infection. When infection did occur, the resulting inflammatory reaction caused the exudation of antibody produced in a secondary response over the cells already infected and immunological damage resulted from the interaction with mycoplasmas closely associated with cell membranes.

Various relatively rare complications of *M. pneumoniae* infection have been mentioned in the review and in numerous other publications, but it is not clear whether they are due to direct infection or to autoimmune reactions. The hemolytic anemias associated with high titers of cold agglutinins seem clearly due to antibodies against the patient's own erythrocytes. Actually the cold agglutinins are only one aspect of a heterophile response in this disease. Complement fixing antibodies most reactive at 4°C with extracts of normal tissue are found frequently in late serum specimens. If such antibodies reach a very high titer it is conceivable that they might, by analogy to cold agglutinins, produce complement mediated tissue damage, for example in the nervous system.

Mycoplasmas found in the genitourinary tract are spread principally by the venereal route. In contrast to the high rate of positive cultures in

adults for T strains and *M. hominis*, these organisms are found much less frequently in children and among groups of adults with restricted sexual activity. In its pathogenicity *M. hominis* resembles some types of infection with pyogenic cocci. Knowledge about disease produced by T strains is recent and still emerging. Antibody titers are generally low in the presence of positive cultures for these organisms, which indicates a carrier state rather than active infection, but in a few cases rising titers or high titers have been demonstrated. Isolation of a T strain in pure culture from the chorion, amnion, and decidua of a fetus with well defined pathologic change suggests occasional intrauterine infection.³ A color reaction dependent on the production of ammonia from urea has been developed for the identification of T strain colonies on agar.⁴ Of some importance with respect to use of antibiotics is the observation that lincomycin is significantly more inhibitory *in vitro* for *M. hominis* than for T strains. The latter, but not *M. hominis*, are very sensitive to erythromycin.⁵

The excitement, several years ago, about the association of mycoplasmas with leukemia has subsided after several different strains isolated from blood or bone marrow were identified as supposed saprophytes or animal pathogens. Since viruses and bacteria can also be similarly isolated at the later stages of the disease, it seems likely that deficiencies in the defense mechanism may account for the results. In my laboratory, cultures in the early stages of leukemia from bone marrow to media or tissue culture gave completely negative results (D. P. Sinha, unpublished). It is of interest, however, that some mycoplasmas show a definite tropism for leukemic cells *in vitro*. With other tissue cultures the significance of alterations in the chromosome pattern by persistent mycoplasmal infection needs further evaluation.

In animals the tropism of some well defined pathogenic mycoplasmas for serosa and endothelium is of interest in relation to similarities between the diseases they cause and human diseases of unknown cause. Mycoplasmas cause arthritis in cattle, goats, mice and birds. In these and other species mycoplasmal infection is associated with peritonitis, pericarditis, endocarditis and chronic vascular lesions. The perfect medium for isolation of human mycoplasmas has

not yet been discovered. It should be remembered that, for a number of years, T strains and *M. pneumoniae* could be grown only in chick embryos until suitable artificial media were devised. Attempts to grow mycoplasmas from human sources in tissue culture are hampered by the frequent contamination of such cultures with non-cytopathic strains. Controls carried without any inoculation are necessary. In choosing tissues to be grown *in vitro* for isolation of mycoplasmas, the probability of success would be greatly enhanced by attention to tropism and host specificity. The optimum would be human embryonic tissue from the same part of the body as that affected in a suspected mycoplasmal disease.

MONROE D. EATON, M.D.

*Senior Scientist in Medical Microbiology
Stanford University School of Medicine
Professor (Emeritus) of Bacteriology and
Immunology, Harvard Medical School*

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A Trial Balloon

THERE IS MUCH TO SUGGEST that the Orwellian age is upon us and that it is arriving more or less on schedule. Take research and development in medicine and the health sciences for example. Medical schools are rapidly becoming dependent upon federal funding for the major part of both their research and educational functions, and federal guidelines and incentives are increasingly indicating the areas where research is to be done and how and for what students are to be trained.

What is to be done is being decided not by educators, or by the professions or even by the public who pays the bills, but by planners in the federal bureaucracy and the politicians who listen to them, who together have control of the essential funds which are now the lifeblood of research and education in the health sciences. Unfortunately the record to date is that they have not been all that omniscient about it. And worse, all the conditions are now present which are necessary to assure conformity, mediocrity and, yes, in a very real sense thought control in research and development (including education) in health care, as federal funds are increasingly distributed through federally controlled channels for federally controlled purposes.

An alternative has been suggested by Jack H. Hall, M.D., to the Association for Hospital Medical Education. He suggests that the health industry should provide for its own research and development (including its own professional education) largely from its own funds. If ten percent of a \$70 billion a year industry were so allocated (which seems about par), \$7 billion would be available annually for medical research, professional education and experimentation in the delivery of health care. He suggests that this money be collected by some sort of use tax upon every aspect of the industry. A percentage would be retained by the originating group, institution or agency for its own research and development purposes, a percentage retained for use at the community, region or state level at their discretion, and a percentage made available for allocation to meet identified needs at the national level. The allocations and expenditures at the various levels would be decided upon with appropriate involvement of all who should be involved in both the public and private sectors, and not always determined by what someone who may or may not know, decides is best for us all. The sums available would have the advantage of being relatively constant and assured, and not so subject to the changing whims of planners and politicians as is so often now the case. And above all, those who are directly involved, and therefore more likely to have direct knowledge of what the real world problems are, and which ones are capable of solution, could have more to say about the allocation of funds for research, education and development for the health care industry.

CASE REPORTS

Refer to: Roon AJ, Mason GR: Surgical management of gastroparesis diabeticorum. *Calif Med* 116:58-61, May 1972

Surgical Management of Gastroparesis Diabeticorum

ANTHONY J. ROON, B.S., AND
G. ROBERT MASON, M.D., *Stanford*

GASTROPARESIS DIABETICORUM was described by Kassander¹ as gastric atony seen in diabetes mellitus. Twenty-one patients with this syndrome have been presented in the literature. All but two of them were treated conservatively, with varying success. Most of the patients showed no significant improvement. Wooten² presented two cases treated surgically with only partial symptomatic relief. Wooten² and Howland³ said that surgical operation may be contraindicated. Our experience includes two cases in which surgical management was effective.

Reports of Cases

Case 1. The patient, a 44-year-old former nurse, was first seen at Stanford University Hospital on May 6, 1965, for nausea, vomiting and weight loss of four months duration. She had had known diabetes for seven years and had been in good health until the onset of that disease, which was in good control on 40 to 50 units of insulin per day and a 2000 calorie diet.

In January, 1965, the patient changed physicians and an attempt was made to control her

diabetes with chlorpropamide (Diabinese®). The disease went out of control, and nausea and vomiting developed, for which she was admitted to hospital and treated with methantheline (Banthine®). Later a streptococcal throat infection developed and she became febrile, dehydrated and acidotic. A 15-pound weight loss ensued. Neuritis developed, with causalgia in the lower back, and urinary hesitancy. Four months before admission to Stanford, insulin injections were resumed. She began to vomit occasionally and was treated with propantheline (Pro-banthine®) with only minimal relief. An upper gastrointestinal series suggested pylorospasm. Urecholine was tried, but because of diarrhea it was discontinued. The patient then was admitted to Stanford University Hospital for further evaluation and treatment. She was thin (signs of recent weight loss) with dry skin and facial hirsutism. There were no microaneurysms in the fundi. The chest was clear to percussion and auscultation; the pulse rate was 110 and blood pressure was 110/68 mm of mercury. Heart sounds were within normal limits. The abdomen was soft and bowel sounds were present. Deep tendon reflexes were depressed and the vibration and position sense was poor.

The urine had a 1 plus reaction for glucose, a trace of acetone, 1 to 3 leukocytes per field, no erythrocytes, no bacteria. The blood contained 10,600 leukocytes per cu mm with 62 percent neutrophils, 19 percent lymphocytes, 9 percent monocytes, 9 percent eosinophiles, 1 percent basophiles and a few macrocytes. The packed cell volume was 37.5 percent and the hemoglobin content 11.6 grams per 100 ml. Electrolytes were all within normal range. Glucose at that time was 348 mg per 100 ml. In 12-hour gastric aspirate volume of 1.15 liters there were 1.8 units of free hydrochloric acid and total acid of 60 units. Serum magnesium was 1.5 mg per liter (normal range 1.5 to 2.4 mg). Histamine-stimulated gastric secretion on June 3, 1965, showed a

From the Department of Surgery, Stanford University School of Medicine, Stanford.

Submitted July 30, 1971.

Reprint requests to: G. R. Mason, M.D., Department of Surgery, Stanford University School of Medicine, Stanford, Ca. 94305.

basal secretion of 13.4 mEq and stimulated secretion of 27.4 mEq of hydrochloric acid. D-xylose excretion was 1.4 grams in 5 hours (less than normal range). Fecal fat was 5.38 grams per 24 hours while the patient was on no fat intake. This value increased to 16.9 grams of fat excreted on a 70 gram fat intake. Examination of stool for ova and parasites was negative on three examinations.

X-ray examination of the upper gastrointestinal tract and small bowel on June 14, 1965, showed relative obstruction at the pylorus (2mm), thought to be functional, as no organic lesions were seen. A motor meal was retained in the stomach ten hours. X-ray films of the lumbosacral spine and knees showed moderate osteoporosis. (Serum calcium at that time was 8.3 mg per 100 ml). The patient was originally treated with suction drainage of the stomach. During the admission period her diabetes was difficult to control and the blood sugar content ranged from 65 to 465 mg per 100 ml. She had several incidents of acetonemia and acetonuria. Nausea, vomiting and diarrhea persisted. It was felt that the diabetes was improperly controlled and that peripheral and autonomic neuropathies were the cause of symptoms. A succussion splash could still be heard and there were several incidents of emesis. Urecholine was tried again and caused diaphoresis and emesis. The patient became depressed over the long stay in hospital and the difficulty in ameliorating her symptoms.

Peritoneoscopy was done June 8, 1965, and no organic lesion was seen. On June 15, six months after onset of symptoms, pyloroplasty was carried out. The postoperative course was good but diarrhea continued—at least five stools a day. Fecal fat studies confirmed the diagnosis of malabsorption. Symptoms slowly regressed and on July 12, 1965, an upper gastrointestinal study showed transit time of approximately two hours with no evidence of obstruction at the pylorus. Three post-operative 12-hour gastric aspirates showed volumes of 365 to 425 ml, with free acids ranging from 20 to 33 units and total acids 40 to 56 units.

The patient was released July 13, 1965, and she had no further problems relative to gastric retention.

Case 2. The patient, a 24-year-old white woman had a 12-year history of diabetes mellitus in fairly good control, with occasional incidents of

coma, but not ketoacidosis. She was maintained on 15 units of regular insulin and 45 units of lente insulin a day. Five months before her first Stanford University Hospital admission, the patient began a diet to reduce from her regular weight of 180 pounds. A month later, nausea and vomiting developed and she was admitted to another hospital and treated with tranquilizers. Her condition was somewhat improved and remained so until, two months before admission to Stanford, nausea and vomiting recurred and acetonuria developed. She was admitted to another hospital for one week but no cause for the gastrointestinal symptoms was discovered. Two weeks before admission to Stanford, nausea and vomiting recurred and the patient was again admitted to a different hospital. Results of liver function tests and of pancreatic screens were all shown to be within normal limits. Pregnancy tests were negative. An upper gastrointestinal series at that time showed an enlarged stomach with delayed gastric emptying. The patient was transferred to Stanford University Hospital on May 23, 1968, for evaluation and treatment of gastric atony.

At the time of admission the patient was taking 35 units of lente insulin. She complained of nausea and vomiting, diarrhea and epigastric pain after meals and had lost 35 pounds in four months. She had been having acetonuria and glucosuria for a few weeks before admission.

On physical examination she was observed to be moderately obese and in no acute distress. Ophthalmoscopic examination revealed evidence of arteriolar narrowing. Several microaneurysms with small hemorrhages were seen. The chest was clear to auscultation and the heart size was within normal limits. Tenderness and distension were noted on epigastric palpation. Neurological examination showed no deficits. It was felt by a psychiatric consultant that the patient had a neurotic component to her personality. Laboratory data were within normal limits. Blood sugar ranged from 110 to 303 during the period of admission. The urine gave a 4 plus reaction for glucose and 3 plus for acetone. Plasma glucose was 174 mg per 100 ml on admission. Gastric analysis showed no free acid in a 13-hour collection. An augmented histamine test revealed a basal acid secretion of 0.7 mEq, which rose to 13.0 mEq with histamine.

An upper gastrointestinal tract study showed delayed gastric emptying, and generalized slow

peristalsis was observed fluoroscopically. A motor meal study showed that the stomach took 12 hours to empty completely.

An electrogastrogram showed normal waves with a slowed rate. After four months of symptoms, Heineke-Mikulicz pyloroplasty was performed. No organic lesions were found. The patient tolerated the procedure well and the symptoms were relieved. A postoperative 12-hour gastric aspirate contained 1.2 mEq of free acid. The patient was discharged a week after operation, asymptomatic. She was taking 35 units of lente insulin and the blood sugar was 200 mg per 100 ml.

On follow-up in our clinic, an upper gastrointestinal series two and a half years after operation revealed no evidence of gastric distention and a histalog test showed a basal secretion of 0.1 mEq and a test response of 15.2 mEq. The patient was still asymptomatic.

Discussion

Gastroparesis diabeticorum as described by Kassander¹ is "asymptomatic" although some of the patients he presented in his paper complained of epigastric fullness and anorexia. These complaints were not diagnostic and the final diagnosis was made from radiologic evidence. It is interesting that 15 of the 21 patients presented in the literature had vague symptoms referable to gastric retention.

Radiologic diagnosis of this entity was discussed by Marshak² and Gould³. The stomach appears grossly distended, with loss of the rugal pattern. This might be interpreted as pyloric stenosis except that the barium can be manually expressed from the stomach, showing that the gastric distension is not due to mechanical outlet obstruction. The transit time of barium is decidedly prolonged (up to 24 hours). Motility of the stomach was decreased in approximately a fourth of these patients and the amount of stomach secretions was greater than normal. These changes are reminiscent of those that occur after vagotomy. Kravetz⁴ observed similar findings at gastroscopy.

Many observers have conjectured upon the pathogenesis of this syndrome. There is a form of gastric atony associated with ketoacidosis but this syndrome is not associated with acidosis. Thus, acute metabolic imbalance cannot be construed to be the cause of this problem.

Dotevall^{5,6} in a study of gastric motility in diabetic patients showed that those with advanced disease had delayed gastric emptying when given saline test meals. Angervall⁷ observed angio-pathic change in the gastric mucosa of patients in whom delayed emptying had been demonstrated. Rundles⁸ in an article on diabetic neuropathy described some diabetic gastrointestinal disturbances as being due to the neuropathic changes in the visceral nerves. Ellenberg⁹ agreed that gastric distension and diabetic diarrhea were both due to visceral neuropathy. Dotevall said that diabetic neuropathic changes of the vagus nerve could account for all the components of gastroparesis. From these observations it would appear that the syndrome is very close to the post-vagotomy state.

Nelsen¹⁰ et al in a study of the motor and electrical functions of the stomach after vagotomy, showed that there is slowing of the electrical and mechanical rates. A desynchronization analogous to atrial fibrillation is present, in which there is ineffective ortho grade flow. Beck and Mason¹¹ showed that a rapid focus of contraction is present in the pyloric antrum and postulated that post-vagotomy stasis may be related to antiperistalsis from this focus. With these experimental models, one can more easily understand how gastric stasis may result from vagal neuropathy.

Conservative treatment for this condition has been recommended in the literature. Howland¹² wrote that conservative therapy is the only valid treatment, and expressed belief that surgical operation is contraindicated. Conservative management consisted of strict diabetic control and a six equal meal diet. Many patients did not respond to this therapy and their symptoms persisted. Wooten¹³ reported two cases in which surgical management was tried. One patient had partial gastrectomy and Billroth I anastomosis because of suspected ulcer disease. He began to gain weight on a six feeding diet after operation. The other patient had pyloroplasty. Although this patient had persistent nausea and vomiting after the operation, epigastric pain was relieved.

The two patients presented here both had pyloroplasty with good results after failure of medical therapy. Follow-up has shown no adverse effects of the operative procedure. Both had significant improvement of the symptoms related to gastroparesis. Neither had a significant alteration in gastric secretion postoperatively. As a result

of this experience we believe that pyloroplasty may be of benefit when conservative measures fail in patients who present with the gastroparetic type of diabetic gastroenteropathy.

Summary

The treatment of gastroparesis diabeticorum recommended in the literature has always been conservative management. Two patients presented herein were successfully treated with pyloroplasty.

This condition is not easily diagnosed on clinical grounds. The radiographic and gastroscopic findings are characteristic. The most likely pathogenesis is related to a diabetic vagal neuropathy.

Pathophysiologically this condition is reminiscent of the post-vagotomy state. The inefficient orthograde propulsion of gastric contents may be facilitated by a surgical drainage procedure, such as pyloroplasty. Surgical management may therefore be considered an alternative to conservative management of diabetic gastric atony.

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Refer to: Friedman E: Symptomatic lower esophageal rings—Treated endoscopically. *Calif Med* 116:61-65, May 1972

Symptomatic Lower Esophageal Rings—Treated Endoscopically

EMANUEL FRIEDMAN, M.D., *San Bruno*

IN A RECENT REVIEW, Goyal et al,¹ summarized results of a variety of therapeutic measures in patients with symptomatic lower esophageal rings. These rings are usually of the mucosal type and frequently are associated with hiatus hernia. Intermittent dysphagia is generally one of the main symptoms. The symptom complex has been called the "steakhouse syndrome"² because often the initial symptoms occur when the swallowing of a large bolus of meat causes temporary obstruction. Delmonico³ in 1956 first reported successful treatment of a symptomatic ring by forceful rupture with an esophagoscope. Subsequently, Somm et al,⁴ using an esophagoscope with external diameter equivalent to a no. 16 bougie, severed one portion of the ring with a punch forceps to relieve symptoms. Norton and King⁵ and Postlethwaite and Sealy⁶ used Hurst bougienage with good results. Adams⁷ and Mossberg,⁸ Hyatt⁹ and Riegel¹⁰ reported good results with pneumatic dilators. Goyal prefers the technique of Hurst bougienage, using first a no. 16 to no. 18 bougie, and following it immediately with a no. 48 without intervening sizes. He believed that procedure preferable to esophagosopic rupture.

In the past few years I have treated three patients with symptomatic lower esophageal rings by esophagosopic rupture of the ring.

Reports of Cases

Case 1. A 48-year-old white woman was seen in October 1965 with a history of intermittent dysphagia over a five-year period. Two and a half years previously, gastrointestinal x-ray stud-

From the Peninsula Hospital and Medical Center, Burlingame.

Submitted November 1, 1971.

Reprint requests to: E. Friedman, M.D., 931 West San Bruno Avenue, San Bruno, Ca. 94066.



Figure 1.— (Case 1) Pre-esophagoscopy radiological picture.

ies were reported as within normal limits. Two years before admission, dysphagia became progressive. It was noted mainly on swallowing solid food and was sometimes associated with lower substernal pain. Two weeks before admission the patient had increasing difficulty swallowing. She said her weight had decreased 10 pounds. Results of physical examination were not remarkable. On radiographic examination a thin, narrow concentric ring was noted at the cardio-esophageal junction, where it reduced the esophageal diameter to 8 mm. (Figure 1.) There was no demonstrable reflux of gastric juice.

Esophagoscopy was carried out with an Eder-Hufford esophagoscope. At 42 cm from the incisors, a protrusion was noted anterolaterally on the right. There was some resistance to the esophagoscope at this level, but with pressure the instrument passed directly into the stomach. Upon withdrawal, the cardio-esophageal junction was well delineated; and at this level a 1 cm long vertical mucosal tear with minimal bleeding was seen. The patient experienced no pain and by the following day was eating well with no dysphagia. Subsequent x-ray studies showed no



Figure 2.—Followup x-ray (Case 1) showing widening of the esophageal ring.

evidence of the previously reported lower esophageal ring (Figure 2). At repeated clinical follow-ups over a period of several years the patient had no difficulties. She regained all the lost weight. Then in March 1971 treatment was required again because of recurrence of the ring.

Case 2. A 54-year-old white man was seen in 1969 with history of two years of intermittent dysphagia and upper abdominal pain. First symptoms occurred at a picnic while the patient was eating steak and they were relieved by the regurgitation of undigested meat. From then on there were recurrent episodes, rarely lasting more than a few hours. X-ray studies done several weeks before admission were reported as negative except for the presence of a hiatus hernia; but at the time of admission to the hospital, a persistent lower esophageal ring was noted (Figure 3.) The patient had lost 14 pounds on a self-imposed diet.

No abnormalities were noted on physical examination. On esophagoscopy examination with an Olympus fibroptic esophagoscope a narrowing of the esophagus was noted 35 cm from the incisors and beyond that point the diaphragmatic



Figure 3.—(Case 2) Lower esophageal ring before esophagoscopy.

pinchcock could be well visualized. Gastric mucosa was seen immediately beneath the narrowing. With slight pressure, there was a mucosal split on the right lateral wall, permitting easy passage into the stomach. No bleeding was noted, and there was no substernal pain. On the following day, the patient had no dysphagia and follow-up x-rays showed improvement of the lower esophageal ring (Figure 4).

The patient was not seen again until November 1969 when he said that dysphagia had recurred about a month and a half after the treatment. X-ray studies showed the esophageal diameter at the level of the ring to be 9 mm. The findings on esophagoscopy were similar to those of the previous examination. Rupture of the ring was again performed without bleeding or pain. X-ray examination on the following day showed the diameter of the esophagus to be 1.8 cm. Anticipatory bougienage with a Hurst no. 44 bougie was started, although the patient was completely asymptomatic, and he was instructed to use the bougie weekly to bi-weekly at home.

The patient has seen the referring physician regularly and has reported no further dysphagia.

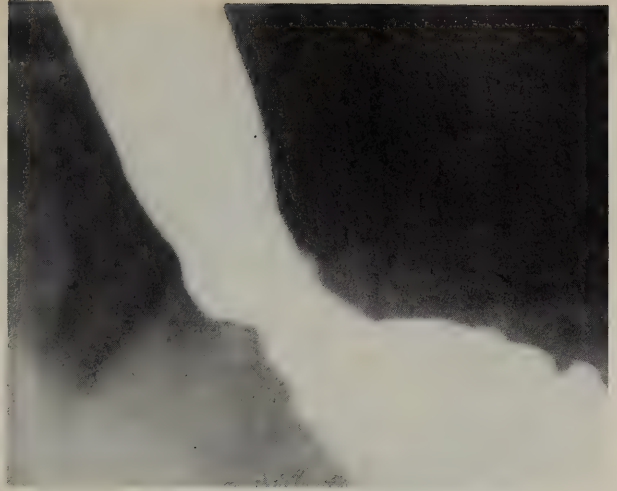


Figure 4.—(Case 2) Radiological film after rupture of ring.

Case 3. A 69-year-old white man was seen in October of 1969 with a four-month history of intermittent dysphagia and a single attack of pain and vomiting. There had been no recent weight loss. The patient had a long history of peptic ulcer disease and two years before admission had had partial gastrectomy. About three months before the onset of the present symptoms, he had had cholecystectomy for stones.

Physical examination was not remarkable. X-ray examination showed a hiatus hernia and a lower esophageal ring (Figure 5).

Esophagoscopy was performed with an Olympus EF esophagoscope. A narrowing approximately 35 cm from the incisors was ruptured with minimal pressure.

A subsequent upper gastrointestinal series including a ciné study showed the small hiatus hernia, and the esophagus was 1.9 cm in diameter at the level of the ring (Figure 6).

The patient returned in May 1970 with obstructive symptoms and x-ray studies showed recurrence of the ring (Figure 7). On esophagoscopic examination the conditions were the same as had been noted in October 1969, and the ring was again ruptured.

Over the next two weeks anticipatory bougienage was done twice with a Hurst no. 44 bougie with no difficulty. He was then instructed in the use of the bougie at home, to be done bi-weekly.

X-ray follow-up examination again showed the ring to be expanded to 1.9 cm (Figure 8). And on clinical follow-up, most recently in February 1971, the patient was asymptomatic.



Figure 5.—(Case 3) Pre-esophagoscopic demonstration of lower esophageal ring.

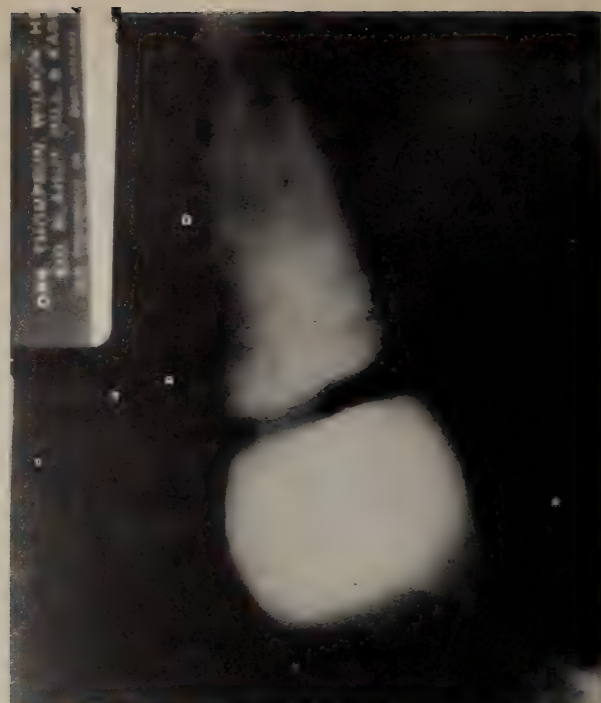


Figure 7.—(Case 3) Recurrence of esophageal ring.



Figure 6.—(Case 3) Widening of esophageal ring following rupture with esophagoscope.

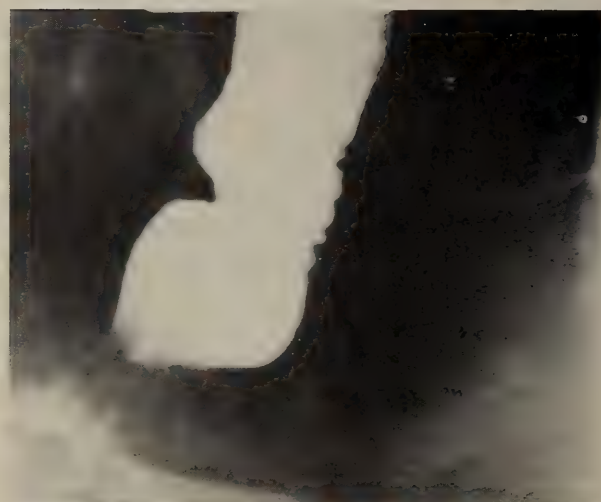


Figure 8.—X-ray film after rupture of recurrent ring by repeat esophagoscopy.

Discussion

Lower esophageal ring of the mucosal type, frequently with the finding of squamous epithelium on the upper portion and gastric epithelium

on the lower, is by far the most common of the so-called lower esophageal rings.¹ Although a ring-like peptic stricture may occur, as could be postulated in Case 3 because of the ulcer history and gastric reflux, one would expect a history of scopolically. But neither history nor direct observation showed any elements of esophagitis in any of the three cases herein reported, and for this reason it is felt that the lesions were the more common type of lower esophageal ring.

Direct bougienage ruptures the ring, especially when done correctly—that is, with bougies of esophagitis and the finding of esophagitis endo-large enough caliber—but visualization of the ring and direct rupture either with the esophagoscope or using Somm's technique⁴ would appear to be preferable, especially when done by an experienced endoscopist. One must consider the hazard of perforation on tearing of the mucosa but it must be weighed against the fact that the problem can be corrected in this way while avoiding thoracotomy or laparotomy. Unquestionably, much more data is needed before the eventual outcome of dilatation or rupture of these rings—by whatever technique—is fully known. A controlled study using initial dilatation or rupture as compared with continued or repeated dilatations on variable schedules would be required to fully elucidate the long-term results. However, there seems little doubt as to the efficacy of rupture or dilatation; and repeat procedures are not so hazardous that they may not be done as required.

Summary

Three patients with lower esophageal rings, treated by esophagoscopic rupture of the ring, have been presented. They required repeat esophagoscopic dilatation after periods of six months to five years; and all were subsequently put on regular, spaced bougienage and maintained in an asymptomatic state.

ADDENDUM: Since submission of this report, two additional patients have been treated in the same manner with excellent clinical response.

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Refer to: Copeland JG, Channick JM, Gittes RF: Complications of a "Mayo enema"—Treatment of resulting hypernatremia and alkalosis. *Calif Med* 116:65-66, May 1972

Complications of A "Mayo Enema"

Treatment of Resulting Hypernatremia and Alkalosis

JACK G. COPELAND, M.D.,
J. MICHAEL CHANNICK, M.D., AND
RUBEN F. GITTES, M.D., *San Diego*

BAKING SODA HAS BEEN USED routinely as a gas-producing agent in enemas for many years.^{1,2} A "Mayo enema" is said to contain 1 ounce of baking soda in addition to 2 ounces of granulated sugar and 8 ounces of water³ and appears to be commonly used.⁴ Complications from this type of enema have not been previously reported. The use of an exaggerated version of such an enema in a critically ill patient in our hospital, however, produced alarming results, pointing out the danger of employing large amounts of sodium bicarbonate in enemas. The abnormalities produced were reversed with emergency measures described below.

Report of a Case

A 28-year-old man with renal failure was being maintained on intermittent hemodialysis. On October 5, 1970, the patient became critically ill with pulmonary edema and required intensive care including mechanical ventilation. It was noted incidentally at this time that he had not had a bowel movement for three days and that his abdomen was moderately distended. For this reason, a "Mayo enema" consisting of "500 ml of

From the Departments of Surgery and Medicine, University of California, San Diego.

Submitted July 7, 1971.

Reprint requests to: R. F. Gittes, M.D., University Hospital of San Diego County, 225 West Dickinson Street, San Diego, Ca. 92103.

TABLE 1.—Serial Laboratory Values

October 6					October 7				
Time	0600	1445	2000	2020	0200	0600	1030		1515
BUN	123		Enema Given			137			37.
Creatinine	5.9					6.4			2.7
Na	137					174			146
K	4.0					2.3			3.8
CO ₂	20					>50			23
Cl	95					98			110
Arterial pH		7.40		7.63	7.70	7.78	7.81		7.45
pO ₂		80		147	82	168	215		71
pCO ₂		35		39	40	34	27		31
%O ₂ by ventilator		100		100	100	100	100		100
Urine vol/24 hours		1460 cc					2090 cc		
Creatinine Clearance		5.8 cc/min					4.6 cc/min		

normal saline solution, 1 cup of baking soda, and 1 cup of sugar" was ordered. This was administered on the evening of October 6, 1970. No return of the enema or bowel content was noted for 12 hours. During this period the patient became slightly somnolent and his metabolic status progressed from normal pH, normal serum sodium and near normal serum bicarbonate to pronounced metabolic alkalosis and severe hypernatremia (Table 1).

Hemodialysis and intravenous administration of 480 mEq of ammonium chloride and 115 mEq of potassium chloride over a six-hour period resulted in reversal of his pH and electrolyte abnormalities to normal. The potassium concentration in the dialysate was 3.5 mEq per liter for the first and 2.0 mEq per liter for the second three-hour period of dialysis. Small cleansing soapsuds enemas were also administered and removed via rectal tube. The patient's state of consciousness returned to normal following this therapy and the episode had no apparent effect on the remainder of his course.

Discussion

One cup of baking soda (bicarbonate of soda U.S.P.) weighs 265gm and contains just over 3000 mEq of sodium and of bicarbonate. When mixed with 500cc of normal saline, this forms a cloudy supersaturated solution-suspension. Given the patient's weight of 51 kg, it can be calculated that slightly over 1000 mEq of sodium and over 350 mEq of bicarbonate were absorbed. The degrees of both hypernatremia and alkalosis present in this patient are often associated with severe neurologic abnormalities and are potentially fatal. Our experience demonstrates that emergency hemodialysis may play a dramatic role in the treatment of hypernatremia particularly in patients with renal insufficiency.

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LETTERS *to the Editor*

This Also for the Ears

To the Editor: Regarding "Eye Drops for the Ears" quoted from Dr. Allen Dekelboum's Audio-Digest tape [Calif Med 116:93, Mar 1972], a suitable preparation to also consider would be fluocinolone acetonide solution (Synalar®, Flunid®) which is made up in a base of propylene glycol.

LEO M. POMERANTZ, M.D.
Beverly Hills

Special Phones for the Handicapped

To the Editor: Physicians, the general public and handicapped people are often not aware of the many helpful services available to them from their local telephone company. The services include two types of telephones for the deaf, one a signal operated flashing answer, and the other with a sending key and receiving vibrating pad. There are aids for people who are hard-of-hearing and those with impaired vision.

Aids for the motion handicapped include special dialing systems, touch tone dialing, headsets and many others. Often the service is especially prepared for the handicapped patient.

A pamphlet "Services for Special Services" is available and every physician should be familiar with these services. For many reasons, not all

telephone personnel know of these aids and you should call the business office and ask for the "communications consultant in marketing." Many telephone companies in California are small but they can obtain consultation from larger companies if they do not have the necessary information available in their own office.

ROBERTA FENLON, M.D.
San Francisco

The Dancing Eyes of Neuroblastoma

To the Editor: The recent excellent article by Finkelstein and Gilchrist on neuroblastoma (Calif Med 116:27-36, Mar 1972) makes no reference to the important cerebellar syndrome of mental change, ataxia and peculiar eye movements (termed opsoclonus) described in many cases of neuroblastoma. The jerky, conjugate but asymmetrical "dancing eye" movements in all directions were first noted in two infants with neuroblastoma by Solomon and Chutorian in 1968.¹ A number of other cases have been described but both the pathophysiology and the neuropathology remain unknown.² The important practical points are that this neurological syndrome be appreciated as an early sign of the tumor, so that appropriate tumor therapy can be undertaken sooner rather than later; and also that the syndrome not be mistaken for metastasis.

FORBES H. NORRIS, JR., M.D.
San Francisco

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Discontinuation of Routine Smallpox Vaccination

To the Editor: In Dr. Shaw's editorial on the discontinuation of routine smallpox vaccination in the March issue of CALIFORNIA MEDICINE, he apparently agreed that routine vaccination of infants should be discontinued but he expressed several reservations. Most of these reservations I believe, were adequately answered in the text of the State Health Department ad hoc committee report which was also published in the March issue of CALIFORNIA MEDICINE. However, several points raised by Dr. Shaw deserve further comment.

1. The conclusion reached by Dr. Shaw that the change in smallpox vaccination policy simply represents a recommendation to abandon *compulsory* vaccination is not an accurate assessment of the situation. The new recommendation states that *routine* vaccination of children be abandoned, and I believe this recommendation goes far beyond the simple abandonment of compulsory vaccination. As a matter of fact, California did not have a state law requiring smallpox vaccination for elementary or secondary school entrance.

2. The problem of rapid recognition and diagnosis of a possible case of smallpox is independent

of the change in smallpox vaccination policy since this problem exists regardless of whether children are routinely vaccinated.

3. The drug methisazone (Marboran®) has not fulfilled its initial promise and the use of this drug at the present time in the control of smallpox is questionable. This drug is not licensed for use in the United States.

4. With regard to the degree of infectiousness of smallpox cases—all cases should be treated as possibly highly infectious, but the data gathered in relation to imported cases to Europe during the past decade show a great variability of infectiousness from very low to very high. Thus, overall, smallpox cases in the modern era are not statistically very infectious, but public health officials and physicians have to consider all cases to be highly contagious and to take precautions accordingly. In 13 of 49 importations between 1950-1971, there were no secondary transmissions. The only example of extreme infectiousness occurred in Meschede, Germany in 1969 where 17 secondary cases occurred in a hospital by what appeared to be airborne spread.

The unresolved and potential problems such as importation and spread of smallpox in this country are basically *independent* of the change in policy, since routine vaccination of children will not prevent the entry of an imported case, nor has this now abandoned routine policy resulted in a well protected general population. At the present time, routine vaccination of children in this country has outlived its usefulness and physicians should now pay more attention to those population groups at higher risk to exposure to smallpox, *i.e.* international travelers and medical personnel.

JAMES CHIN, M.D.

Chief, Bureau of Communicable Disease Control
California State Department of Public Health

102nd Annual Session
California Medical Association
March 10 to 14, 1973
Disneyland Hotel
Anaheim

Government and Medicine

Five Years of Medicare in California—Problems, Resolutions and Prospects

MERCIA LETON KAHN, *San Francisco*

"BY CRACKY, IT WORKS!" was the comment of a surprised gentleman in a cartoon about Medicare sent to me by one of our beneficiaries in the very early years of the program. We have our problems now, as we did then, but the cartoon still encourages all of us in our efforts to respond positively to the changes and problems in the delivery and insurance of health care. Recently, I received a letter from a physician who explained that a 67-year-old man suffered from an end stage polycystic renal disease which would require a continuing hemodialysis program. The physician was considering advising his patient to buy a dialysis machine for home use, but wanted to know whether the machine and services would be covered under Medicare. I was able to advise him, "Yes, most of the expenses can be covered under Medicare" and was pleased that the Medicare coverage of the relatively novel home dialysis equipment not only would conserve Program expenditures but also would help to promote the personal comfort and security of his patient.

Our efforts to promote more efficient claims processing and more refined health insurance benefits to the elderly depend very much on the co-operative dialogue between those in the medical professions, the health insurance industry, and the various government offices involved with the publicly funded health insurance programs.

The author is Regional Representative, Bureau of Health Insurance, Social Security Administration, San Francisco.

Submitted March 13, 1972.

Reprint requests to Bureau of Health Insurance, Social Security Administration, 50 Fulton Street, San Francisco, Ca 94102.

When I was asked to write this article, I wondered at first whether I really should dwell on some of the problems rather than on some of the successes of Medicare. However, on the day the invitation to contribute to this journal was extended, my in-basket reflected several of the problems which continue to trouble us: a memorandum expressing concern that several convalescent hospitals may no longer meet the Medicare Standards of Participation; a report of a meeting which had been called to encourage more effective utilization reviews; a letter from a physician who objected to the "reasonable charge" allowed for his services; a letter from a son who complained of a denial of reimbursement for part of his mother's stay in an Extended Care Facility (ECF). These and similar issues which all of us work with daily indicated that even on issues we believe are resolved, misunderstanding is prevalent so that we must continue to work with our "old" problems while anticipating and working for the resolution of our newer problems.

In an article for this journal in October 1968, "Medicare's Experience with Medicine," I outlined the earlier national and regional efforts made to eliminate unnecessary paperwork, simplify claims forms, and promote the promptest payment of benefits consistent with a thorough review of the claim. Both the government and the insurance companies which process Medicare claims recognized the need for much closer coordination if those and other goals of the Pro-

gram were to be achieved at an acceptable cost. In 1969 the Bureau of Health Insurance and the insurance companies, who, incidentally, we term "contractors," were committed to a policy of increased liaison and communication, which had continued to expand and improve.

Realizing that truly effective communication requires proximity and rapport, the Bureau in 1969 introduced to our contractors carefully selected "Resident Health Insurance Representatives," each of whom would work on-site with a contractor. In California a resident representative was stationed at California Blue Shield and at Occidental in July 1969. Later in the spring of 1970, resident representatives were also appointed to work on-site with the Blue Cross Plans in Los Angeles and Oakland. Each of the three other contractors which process Medicare claims in California, Aetna Life and Casualty, Mutual of Omaha, and Travelers Insurance Company, has a resident representative located in its home office.

The Health Insurance resident representatives work very closely with the contractors in monitoring and reviewing the claims process, and act as the daily personal liaison for the Bureau of Health Insurance Regional Office. To assist the resident representative in his work, my staff has expanded in the past three years to include such highly trained specialists as accountants, systems analysts and a nurse, all of whom provide knowledge and skills previously not available to us regularly.

As part of the national goal of decentralizing the day-to-day administration of HEW's many programs, the field organizations of which we are a part were reorganized and delegated additional responsibilities and authority. We are now involved to a much greater extent in regional contract negotiations, budget approvals and contractor performance appraisals, all of which reflect the closer liaison we have established during the last three years.

One of our more recently assumed responsibilities is that of program evaluation and validation, for which we have established a branch under the direction of a program officer. The Program Evaluation Branch investigates possible program abuse or potential fraud situations and when necessary refers serious violations of the law to the United States Attorney.

Fortunately, many of the complaints which are investigated are really the result of a misunderstanding of the Medicare law and frequently are resolved, without legal action, during on-site visits to the provider, supplier or physician. Occasionally, we have no choice but to seek court action, and in California four criminal convictions have been returned and four indictments are currently pending.

We feel that our reorganization and more specialized staffing has equipped us to handle the increasing volume of Medicare claims and expenditures. From Fiscal Year 1967 to Fiscal Year 1971, for example, the national Medicare expenditure increased from \$3,394,000,000 to \$7,825,000,000, and California more than exceeded the national growth; in Fiscal Year 1967 total Medicare expenditures in California were \$398,147,000, increasing to \$836,914,000 in Fiscal Year 1971. The increasing expenditures reflect, of course, an increasing claims volume, which has proved to be beyond anyone's expectations. The volume of Part B claims for physician and supplier services in California has increased from 514,000 in January 1968 to over 750,000 in January 1972. The number of claims processed in California exceeds the total of all states in some regions, and we expect a significant increase of volume in California during the coming fiscal year.

Table 1 shows some related data from 1967 through 1970 indicating the increase in many aspects of the program both in usage and money spent.

The very large enrollment, more than 1,776,000, of Medicare beneficiaries in California (the state continues to attract retired persons) is generating the high claims volume, which in turn magnifies the complex problems of program administration. One of the most persistent problems in Medicare's early years in California was the complaint of slow claims processing. Initially, California Blue Shield was the Medicare carrier for all but Los Angeles and Orange Counties, which were served by Occidental Life of California. To distribute the workload more efficiently, the contract of California Blue Shield was amended, effective January 1, 1970, to provide Occidental the responsibility for processing claims for services rendered in seven additional counties in Southern California. California Blue

TABLE 1.—Selected Data From the Medicare Program

Item	1967	1968	1969	1970
Persons enrolled as of January 1 for:				
Hospital insurance (HI)	1,650,701	1,690,476	1,731,020	1,765,564
Supplementary medical insurance (SMI)	1,569,481	1,602,305	1,677,116	1,726,323
HI and/or SMI	1,653,373	1,693,539	1,737,784	1,776,548
Amounts reimbursed during the fiscal year:				
HI: Total (in thousands)	\$286,290	\$411,390	\$543,740	\$544,039
SMI: Total (in thousands)	\$111,857	\$202,698	\$228,512	\$292,875
HI: Amount per HI enrollee	\$175	\$243	\$314	\$308
SMI: Amount per SMI enrollee	\$72	\$127	\$136	\$170
Participating facilities as of July:				
Number:				
All hospitals	590	586	581	582
Short-stay	521	527	525	527
Tuberculosis	4	3	3	3
Psychiatric	38	37	34	33
Other long-stay	27	19	19	19
Extended care facilities	739	851	921	962
Beds:				
All hospitals	117,581	105,754	94,856	95,130
Short-stay	65,045	62,502	63,394	64,893
Tuberculosis	391	296	295	295
Psychiatric	42,785	35,816	24,402	23,086
Other long-stay	9,360	7,140	6,765	6,856
Extended care facilities	51,728	62,246	69,249	78,900
Beds per 1,000 HI enrollees:				
Short-stay hospitals	39.4	37.0	36.6	36.8
Extended care facilities	31.3	36.8	40.0	44.7
Home health facilities	92	99	103	108
Independent laboratories	571	582	612	626
Admissions (in thousands) during the fiscal year:				
All hospital inpatient admissions	421	470	510	518
Extended care facility admissions	30	76	91	96
Admission rate per 1,000 HI enrollees:				
All hospital inpatient admissions	254.9	277.8	294.3	293.3
Extended care facility admissions	18.4	45.0	52.5	54.1

Shield retained responsibility for all Medicare claims in which Medi-Cal was involved, and the Travelers Insurance Company continued to process the Medicare claims for beneficiaries of the Railroad Retirement Board.

The redistribution of the California Medicare claims has proved a wise decision, particularly as the number of claims continues to increase. California Blue Shield now processes a claim workload greater than ever before; it received 474,000 claims in January 1972, while Occidental received 233,655. In April 1969, for example, our carriers averaged 5.2 weeks' work on hand, 67.4 percent of which had been pending longer than 30 days; in November 1971, the average volume of claims pending was 2.2 weeks' work on hand, of which only 12.4 percent had been pending more than 30 days.

Significant Issues and Problems

While the claims backlog has been brought under firm control by our carriers, one trend which could affect claims processing efficiency seems to be developing—a decrease in the rate of assignment acceptances by physicians and suppliers. An acceptance of assignment is, as you know, the election by a physician or supplier to receive Medicare reimbursement directly from the carrier. We encourage a physician or supplier to accept assignment, as both he and the patient feel more secure knowing that the medical bills will be paid directly and the carrier is able to process the claim more efficiently and quickly because the form usually is more thoroughly completed. The decrease in assignment rate increases both claims processing time and cost. In this region for fiscal year 1968 the proportion of

assigned claims was 73.2 percent but for January 1972 the assignment proportion had dropped to 50.2 percent.

The use of assignment creates some problems, but they can be resolved easily by a greater understanding of the obligations accepted with assignment. Under the law, acceptance of an assignment obligates the physician or supplier to accept the carrier's determination of the allowable charge for a service as his full charge for that service. For services reimbursed under the assignment agreement, the physician or supplier may not bill his patient for any more than the difference between the *allowable charge* determined by the carrier and the payment received from the carrier. Occasionally, we learn of violation of the assignment agreement, when a beneficiary is billed for the difference between the charge made and the charge allowed, but usually a brief explanation of the obligations of assignment to a physician or supplier and his billing clerk quickly resolves the misunderstanding.

Reasonable Charge

The misunderstandings related to the assignment agreement result from a reduction of the charge for a service, as each of our carriers prices services and procedures under "reasonable charge" screens. The customary and prevailing screens are calculated from the actual charges made by physicians for different procedures in a period of time long enough to establish the charge as "customary." The screens are recalculated periodically, and recently were recalculated twice in one year. On January 1, 1971, the screens were recomputed to include charges for services during 1969. Six months later the screens again were recalculated to reflect charges made for services during 1970 and the new screens were effective July 1, 1971. We are scheduled now to update the reasonable charge screens annually on July 1.

All of us are concerned about the rising costs of medical care, and Congress has expressed an intention to align an increase in reimbursement of physician's fees with the overall cost of living. Section 224(a) of H.R. 1* as passed by the House of Representatives, and currently pending in the Senate, would provide that prevailing charge screens would be increased effective each

July 1, but only to the extent justified by the application of selected economic indexes to actual charges made during the year. The economic indexes would be selected to reflect increases in the costs of providing medical care, establishing an equitable measure of the "reasonable charges" for medical care.

Another development related to reasonable charges is the increasing use of different terminology systems for coding Medicare claims. The Bureau of Health Insurance has been working closely with various organizations in an attempt to develop a uniform procedural coding and terminology system that would be acceptable nationwide to the major users of such a system. The necessity of an accepted procedural coding system was demonstrated very early in the Program when the California Relative Value Study (CRVS) was invaluable to us in developing acceptable customary and prevailing charge screens. The refinements of the 1969 CRVS coding system permit more precise coding and identification of the procedures performed, but until the fiscal effect of a revised coding system can be determined, only the two carriers in California are authorized by the Bureau to use the 1969 CRVS.

As my discussion has indicated, the cost of Medicare is a very real concern which affects not only providers, suppliers and physicians, but beneficiaries, most of whom live on fixed income. On July 1, 1972, the premium for Supplementary Medical Insurance will be increased from \$5.60 to \$5.80 a month. The premium increase is the lowest in recent years, reflecting economies attributable to Price Commission guidelines and savings in Program expenditures from increased carrier claims review for covered services, reasonable charges, program abuse, and fraud. We are continuing to work with our carriers, for example, to establish controls on claims payments, to detect duplicate charges, and to recover any overpayments made. In recovering overpayments, we have received fine cooperation from the medical community and the beneficiaries in this region, as 49 percent of overpayments discovered are reported by the physician or beneficiary. The post-payment reviews and internal audits by carriers account for approximately 30 percent of the overpayments detected.

*HR-1 is the legislative proposal to amend both the Social Security and Medicare provisions. The bill has passed the House of Representatives and is currently pending before the Senate.

Medical Foundations

While striving to conserve Program expenditures through increased cost control, we are equally concerned that Medicare should work with the medical community to help provide high quality medical care. Since early 1969, several Foundations for Medical Care in California, such as those located in San Joaquin, Kern, San Diego, and Marin Counties, have entered into sub-contracts with Occidental Life and California Blue Shield and have given valuable assistance to those two California carriers by providing medical, utilization, and local peer review of Medicare claims. The foundation review includes an examination of the reasonableness of the charges and the medical necessity for the services provided, both of which involve difficult and sensitive judgments. Under the Medicare law, only services which are reasonable and medically necessary in relation to the physician's diagnosis are reimbursable, and in any medical review of a claim, whether performed by a foundation or by a carrier's medical consultants, thoroughness of the diagnostic and treatment information provided by the physician on the claim is essential to arriving at a sound coverage determination consistent with the provisions of the law.

Extended Care Facilities

Particularly difficult problems with coverage determinations involve extended care facilities (ECF). Especially significant is the effect that retroactive determinations or lack of reimbursement for a stay in a facility has on the patients and their families and the related effect on the physician who placed the individual in the facility. In an attempt to remedy the often devastating individual financial burden caused by determinations of this type, the Administration has initiated the assurance of payment procedure which is now used by about 50 percent of the ECF's in California. Under this procedure, an ECF may submit pertinent medical information to the intermediary when admitting a patient for whom Medicare coverage is questionable. The intermediary will review the medical data and, within 48 hours, advise the ECF by telephone or telegram whether the patient stay may be covered. Until the ECF is advised of this determination, payment for care is assured. The procedure requires effective communication between

the physician, the facility and the intermediary to minimize denial of payment after admission. All in the health care professions are striving to identify non-covered levels of care at admission, as evidenced by a California Medical Association House of Delegates resolution in 1971 which called for component society involvement in furthering assurance of payment.

Much of the success of assurance of payment depends on the understanding the physician has of the Medicare "level of care" provisions. For ECF services to be reimbursed, one critically essential condition for covered "level of care" is the medical need by the patient for "skilled nursing services on a continuing basis." Identifying covered level of care requires distinguishing between "non-skilled" service and the "skilled services" which may be reimbursed. One principal problem in making the distinction arises when the patient requires the care provided in an ECF, possibly because he is too feeble to care for himself or has no one to care for him at home, but does not require *skilled* nursing services on a continuing basis. In these circumstances, the Medicare law does not permit payment for care in an ECF.

Advising the patient or his family that institutional care is needed but may not be reimbursed by Medicare, and gaining his acceptance of the coverage limitations, is no easy task. Primarily because of difficulty of such judgments, one of my staff wrote an article on level of care, "A Few Things You Always Wanted to Know About Medicare,"* that is available from my office and is of great assistance in understanding the Medicare "level of care" coverage. One other source of information concerning level of care is the Los Angeles County Medical Association *Bulletin*, which has published articles on both extended care facility and home health agency coverage.

Utilization Review in the Institutional Setting

Identifying covered levels of care is an equally difficult, if not more controversial, problem for institutional utilization review committees. I and my staff frequently are asked, "How can an intermediary deny claims for which the attending physician and the Utilization Review

*SS Publication 62-71 (6/71) "A Few Things You Always Wanted to Know About Medicare"

Committee recommend continuation of the patient's stay in the institution?" The primary answer is found in the different roles assumed by the physician, the Utilization Review Committee and the intermediary: The physician and the Utilization Review Committee recognize that the patient needs some degree of institutional care for his medical needs, yet the intermediary, while not questioning the medical decision, must determine whether the level of care need is the intensive "skilled nursing care" reimbursable by Medicare.

Whenever this question commands my attention, as it does quite frequently, the proverb that "a journey of a thousand miles begins with a single step" comes to mind. As early in the Medicare Program as 1967, the American Medical Association was the host at a meeting to discuss pertinent issues involving utilization review and published a guide for medical societies to use in assisting medical staffs in performing utilization review responsibilities. Considerable progress has been made in clarifying matters about which there was confusion, particularly those relating to acute hospital inpatient stays, but more effort is needed to bring about a more precise understanding of what constitutes covered ECF care in order to minimize the recurring problem of retroactive denial of ECF stays. Many of our significant advances have been realized when the local medical society supports utilization review and emphasizes it as one of the essential elements of high quality patient care. Unfortunately, the record of achievement is not uniformly high in California, for in some counties the medical society is not yet wholly supporting increased utilization review.

To find new methods for improving the quality of care through utilization review, the Bureau of Health Insurance is working closely with the county medical societies in California, experimenting with various approaches to utilization review. We are paying the costs of three county medical societies which are each providing utilization review to ECF's in a different manner:

Los Angeles County Medical Association District 12 has two physicians who meet weekly to review medical abstracts of extended duration cases prepared by the district's medical librarian and to review questionable admissions. At a monthly meeting of the full seven-man commit-

tee, discussions are held concerning trends, problems, studies, and sample reviews. The medical record librarian abstracts appropriate information needed to prepare profiles of the facilities and to conduct various studies as recommended by the committee.

The Riverside County Medical Association performs utilization review through a sub-committee which meets monthly in each facility to review the entire medical record of all Medicare patients. In addition, a member of the sub-committee visits the facility as appropriate to review extended duration or questionable admission cases.

The Santa Barbara County Medical Society sends a committee to each facility twice a month to review all Medicare patients' charts. An executive committee meets weekly to review denials made by the sub-committee, and to review any questionable admission cases not seen by the sub-committee, while the full utilization review committee meets monthly to discuss problems and issues needing clarification.

Both the Riverside and the Santa Barbara societies are participating in an extended care facility project conducted by the Hospital Utilization Program of Western Pennsylvania and they are compiling statistical data which will be used by the society committees.

Not all questions concerning extended care facilities pertain to level of care. The Bureau of Health Insurance is now the regional focal point for the Department of Health, Education, and Welfare in receiving and analyzing complaints about services in hospitals, ECF's and home health agencies. Whenever a deficiency is found in a provider certified by Medicare, we work with the provider and the state agency to correct the deficiency if at all possible. As a last resort, the Medicare certification may be terminated, and in that event the provider is no longer eligible for Medicare reimbursement.

The involuntary termination of certification of providers, particularly of ECF's, has become much more frequent in the last two years. The sub-standard conditions of some extended care facilities has been of great concern nationally, and the President has initiated a program to improve the standards of nursing homes and other facilities which are participating in federal programs. My office has joined with the Medical Services Administration and the Health Services

and Mental Health Administration of the Department of Health, Education, and Welfare in encouraging and accelerating actions to assist the states to improve their capability to survey hospitals. One of our goals is to strengthen the federal procedures for monitoring the survey and certification process for both Medicare and Medi-Cal and to insure that acceptable standards are maintained in all certified facilities.

Prospects

Considerable creative energy is being devoted to the problems of health care delivery providing dynamic, fresh approaches to expanding the availability of quality medical care. New thoughts on medical education, the use of paramedical personnel, rapidly advancing technology, such as the home dialysis equipment mentioned earlier, are all presenting demanding challenges to those of us concerned with health care and insurance. In 1967, Congress passed legislation authorizing the Secretary of Health, Education, and Welfare to engage in experimental methods for improving the Medicare reimbursement of covered health services, to which the health care community and insurance industry in California has responded enthusiastically.

Blue Cross of Southern California proposed, and the Secretary of HEW approved, an experiment designed to encourage savings in labor costs by hospitals. In the experiment, hospital efficiency in a sample of 25 Southern California hospitals is being measured by comparing labor performance with performance standards scientifically established by the Commission for Administrative Services in Hospitals (CASH). The incentive to the participating hospital is a share of the savings realized by improving labor efficiency and productivity. The start-up costs and first incentive year of the experiment were funded by the Kellogg Foundation and Blue Cross of Southern California, but since April 1, 1971, the Social Security Administration has been providing financial support, which will cover the second and third incentive years and the time needed for analysis.

A second experiment in which we are engaged in California is the extension of the principles of the Certified Hospital Admission Program (CHAP) to Medicare in facilities in a five-county area. Included in the experiment will be the admissions to hospitals, and ECF's and home

health agency visits, and the primary objective is to promote quality medical-care with appropriate cost and utilization controls.

Legislation now pending, if enacted, will further the expansion of Medicare coverage and the authority to support novel health care delivery systems. Some of the provisions are:

- An option for Medicare beneficiaries to choose to have all covered care provided by a health maintenance organization
- Authority for experiments and demonstration projects in prospective reimbursement
- Authority for the Secretary of Health, Education, and Welfare to terminate or suspend Medicare payments to suppliers of health services found guilty of program abuse
- Extension of Medicare coverage to persons entitled to at least two years of disability benefits under the Social Security or Railroad Retirement Programs.

Congress in particular has expressed a concern that the unmet need for health insurance protection among our nation's disabled workers should be met as soon as possible. About 1.5 million disabled beneficiaries would be eligible for both hospital and medical benefits under Medicare, and if this provision is enacted, approximately 1.85 billion in benefits would be paid on behalf of disabled workers in the first full year after enactment.

I have pointed out a few of the problems and a few of the solutions in the first five years of Medicare in California. If I were asked to cite the Number One problem, I would say the need for better understanding of what the law provides. An example in a recent nationwide survey* of public awareness and knowledge of Social Security programs is alarming, to say the least. To the question, Does Medicare pay for ECF bills even if a person is *not* sick, 44 percent said yes or that they were not sure. And to the question, Does Medicare pay doctor bills only to patients in an ECF or hospital, 53 percent said yes or that they were not sure. Changes which are sure to come will complicate even more the communication problem, but it is hoped that some of the changes will serve to simplify. Our efforts toward better communication between the medical community, the health insurance industry, and the over-65 for whom the program was enacted, must be intensified.

*Major findings of the 1971 Nationwide Survey, Social Security Administration, Office of Public Affairs, SS Publication 94-71 (9-71)

In the Forefront

Closing the Communication Gap in Cancer Care

SAMUEL R. SHERMAN, M.D., *San Francisco*

THE INTENT OF PUBLIC LAW 89-239 (Heart Disease, Cancer and Stroke Amendments) was to narrow the gap between what was known and what was done in the management of the three killer diseases, heart disease, cancer and stroke. Since implementation of this law, under the aegis of the Regional Medical Program (RMP), many proposals were presented, authorized, and funded relating to the conquest of heart disease and the prevention and treatment of stroke. Similar proposals for cancer were expected, but did not materialize in any significant amount. In spite of the interest and urging of local branches of the American Cancer Society, there still existed a wide communication problem between the potential cure and the real cure of this disease. This gap applied equally to practicing physicians and potential patients and explained the reluctance of planning efforts in developing and submitting Regional Medical Program proposals in the cancer category.

More than one third of all cancer patients in the United States are being saved today. To the optimist this is reassuring, but to the pessimist it is distressing.

The Area I planners of the California Regional Medical Programs, working closely with the Cancer Society representatives, decided on a positive and aggressive approach to the problem of providing comprehensive care to cancer patients in Northwestern California. More importantly, whenever feasible, this care would be made available in the patient's own community.

The author is Cancer Coordinator of California Regional Medical Programs—Area I.

Reprint requests to: S. R. Sherman, M.D., California Regional Medical Programs—Area I, University of California, San Francisco, San Francisco, Ca. 94122.

Within Area I, two medical facilities, the University of California, San Francisco and the Claire Zellerbach Saroni Tumor Institute of Mount Zion Hospital and Medical Center, possessed broad based oncology programs; and although they are geographically and administratively separate, they have previously cooperated in joint programs of cancer education, research and patient care. These cancer centers pledged their resources, personnel, equipment, and expertise to a joint effort to extend their services in a broad based cancer educational program involving dozens of peripheral institutions and medical groups. The services of both cancer centers were further crystallized by the formation of a Cancer Coordinating Committee and appointment of a Cancer Coordinator.

In order to meet the needs of the patients of Area I with current resources, four major subprograms were implemented to enable more effective utilization and extension of the available resources.

1. The first subprogram was the Clinical Cancer Consultation Service which provides consultant teams to participating hospitals. If a hospital did not feel that it required a complete cancer management team, it would have the option of receiving aid from any particular specialists desired. These include radiation therapy, chemotherapy, surgery, nuclear medicine and the social sciences. Physicians and paramedical consultants would be available to attend local tumor boards biweekly or monthly or to attend clinics and treatment sessions in their specialties. Members of the Cancer Consultation team would also assist personnel at the participating hospitals to

develop their own program, particularly programs in cancer chemotherapy and radiotherapy. The members of the team would provide advice on the construction of facilities; architectural consultation would also be made available. The educational opportunities accessible to local personnel were stressed; these teams also actively attempted to attract prospective trainees to the ongoing preceptorship programs at the established cancer facilities.

2. The second portion of the program was a radiological physics service. This program was devised to assist the available radiotherapy resources to use their present equipment in an optimum fashion, applying the modern radiotherapeutic techniques. Because of the extreme shortage of radiation physicists and equipment, it was evident that a regional effort would lead to a more rapid and adequate provision of these services. Certain installations could not afford to employ a full time radiation physicist; this could be solved by the use of a regional program. In addition, the pooling of resources would enable the use of sophisticated computer techniques to solve many problems which previously required hours of laborious hand calculations.

3. The third portion was a computerized data retrieval service. This system eventually will be provided to participating hospitals on request and will serve as a memory bank of information about individual patients treated by means of radiotherapy, chemotherapy and surgical operation. It will be possible to put many informational items about each patient into computer tapes and on short notice to retrieve current information on the results of a given treatment technique in one hospital as compared with the region as a whole. This service will enable the individual hospital to evaluate its own performance in the cancer field. The data retrieval service will also act as an important part of the overall evaluation of this regional program. It is anticipated that both the data retrieval and the regional medical physics programs will serve to meet continuing needs for many years to come.

4. The fourth portion consisted of an educational program for medical, paramedical and lay public. Educational aspects were, of course, included in each of the other three subprograms and it was probably within those portions of the

program that the greatest opportunity for education occurred.

During the almost two years of the program's activities, literally hundreds of radiotherapy consultations were made by personal visits to local hospital radiotherapy departments, radiologists' offices, tumor board meetings and cancer seminars (away from the medical centers). Likewise consultation on request was provided regarding the need for special or additional radiotherapy equipment and the appropriate equipment when indicated.

Radiophysics consultations* for dosimetry determinations and equipment calibration far exceeded expectations. Treatment planning via computer and tele-communication between peripheral and central institutions became commonplace.

Tumor boards were formed where none previously existed, and flourished with the input from the visiting specialists in chemotherapy, radiotherapy, surgical and gynecological oncology. Existing tumor boards were enhanced and augmented in the same manner. The rotating tumor board concept proved extremely valuable in large counties with multiple hospitals having different staffs. As a result of these educational activities, more interest was generated locally in the comprehensive management of cancer patients, including their non-medical needs.

The computerized data retrieval system was refined and tested in the second year of the program and soon will be implemented in several San Francisco Bay Area hospitals for further testing. Following this phase, it may be adopted by any cancer service in the nation.

Several unexpected spin-offs have resulted from the overall cancer program. The exposure of the visiting cancer consultants to the physicians in peripheral communities inspired the formation of the Northern California Academy for Clinical Oncology. The membership of this organization had a common interest—the care of cancer victims. At last count there was a total of 150 radiotherapists, chemotherapists, surgeons, gynecologists, generalists and internists on the referral roster. About 100 regularly attend the quarterly scientific sessions held in San Francisco. These meetings have afforded interchange of the latest information on all aspects of cancer and thus serve a most useful purpose.

*Approximately 50 such visits were made per month.

It was at one of the early meetings of this group that the need for training programs for radiotherapy technologists and nuclear medicine technologists and technicians was enunciated. After documentation of this need and verification of future job opportunities, discussions were held with the appropriate educational institutions and commitments were obtained that resulted in positive action.

The radiotherapy technologists training program is in operation at San Francisco City College with 13 trainees. Clinical instruction for one year will be given at the University of California, San Francisco and the Claire Zellerbach Saroni Tumor Institute, Mount Zion Hospital.

The nuclear medicine program is still in the curriculum development phase because of the necessity of involving both a two-year and a four-year educational institution in the academic portion of the training. Clinical and laboratory instruction will again be given at the University of California, San Francisco, and Mount Zion Hospital.

Another spin-off is the adaptation of the team approach to cancer management. The realization that cancer is a complex disease and that many effective methods of treatment are now available has resulted in the use of a variety of health professionals working in close cooperation. Both the patients and the healers profit from this arrangement.

The accomplishments of the program to date are measurable, both quantitatively and qualitatively. Written reports from the users of the services have indicated that many more patients have been seen at tumor boards than previously, many more local physicians have attended tumor board meetings, and many more patients have received earlier and more effective treatment in their home localities as a result of these activities. Furthermore, the treatment has been given with greater confidence by their own physicians.

In summary, then, the efforts of two enlightened cancer centers to spread their knowledge and their techniques to other and often far away groups were described in this article. The vehicle making these efforts possible was the Regional Medical Programs. Although the cancer component of RMP has not been as "popular" as the other categories, this Area I Cancer Program is an example of what can be done rather inexpensively and most effectively.

What, then, can be held in prospect for the future in RMP supported cancer programs in Area I? A proposal now in preparation which would continue the above mentioned programs on a cost recovery or charge basis. This would allow for partial funding of new programs hitherto not in existence and requested by the users of the previous program. These would include:

1. Health Manpower Training
 - a. Augmentation of the radiation therapy technology training with provision of a full time coordinator, based at San Francisco City College.
 - b. Training of cancer social workers and social work assistants for cancer counseling.
 - c. Tumor registry training program to enable physicians and non-physicians to make better use of tumor registries.
 - d. The training of general oncologists for the joint practice of radiation therapy and chemotherapy.

2. Application of the Team Concept in Cancer Care

A series of conferences for nurses, social workers, Cancer Society staff members and volunteers, nursing students, physicians and dentists will be held. The use of "mock" tumor boards and patient counseling sessions will help to demonstrate the techniques necessary to accomplish this objective.

Medical Jurisprudence

Minors and the Physician

Effects of the Law Lowering the Age of Majority

JOHN I. JEPSEN, Esq.,* *San Francisco*

SUBSTANTIAL CHANGES HAVE occurred in California law concerning the medical care and treatment of minors since the publication of the article "Minors and the Physician" in the December, 1970, issue of CALIFORNIA MEDICINE. This article will review those changes which have occurred.

Assembly Bill No. 2887 which became law March 4, 1972 amends a number of California laws by lowering the age of legal majority, for most purposes, to 18. (California residents between 18 and 21 years were given the right to vote in California by a law passed in 1971.) In this state a person 18 years old or older will be considered of the age of majority for all purposes except the following:

1. Sentencing and commitment of persons to the youth authorities (California residents between 18 and 21 may still be committed to the control of the youth authorities);
2. For veterans' benefits (veterans' benefits are not available to persons under 21 years of age); and
3. For the purchase of alcoholic beverages (California residents under the age of 21 cannot purchase alcoholic beverages).

Until March 4 of this year, California law defined a minor as any person under the age of 21 who was not legally married after his 18th birthday. Under the new law, now in effect, minors are defined as "all persons under 18 years of age."

*Of the firm of Hassard, Bonnington, Rogers and Huber, Legal Counsel to the California Medical Association.

Submitted February 3, 1972.

Reprint requests to: Mr. J. E. Curley, Jr., California Medical Association, 693 Sutter Street, San Francisco, Ca. 94102.

Hence any person 18 years old or over will be able to give a legally valid consent to the rendition of medical or surgical care by a physician. Therefore a physician and surgeon in the State of California need only obtain the informed consent of his patient whenever treating anyone 18 or over.

However, with respect to patients under the age of 18, a physician must still obtain the informed consent of the parents or guardian of the patient before rendering medical or surgical treatment to the minor, unless a well-defined exception, recognized by California law, is applicable. These exceptions were discussed at length in the earlier article appearing in the December, 1970, issue of CALIFORNIA MEDICINE.

The first exception concerns the ability of an unmarried, pregnant minor to give a valid and legal consent to medical treatment related to her pregnancy. At the time the original article, "Minors and the Physician," was published, there was some question in the State of California as to whether a pregnant minor could consent to an abortion.

This question was settled by the California Supreme Court in May of 1971, in the matter of *Ballard vs. Anderson* (4 Cal.3rd 873, 1971). In *Ballard vs. Anderson*, the California Supreme Court, by a 4-to-3 decision, held that under California law a pregnant minor of any age, who is able to convince competent medical authorities that she has the requisite understanding and ma-

turity to give informed consent, can legally consent to an abortion. It should be noted that the Supreme Court decision requires the physician to be convinced that the pregnant minor is mentally capable of and does in fact understand the nature and consequence of the procedure to be undertaken.

Married persons under the age of 18 are still capable of rendering a valid consent for hospital and medical care. This ability will continue even though the minor obtains an annulment or divorce before reaching age 18. Furthermore, minors or individuals under the age of 18, on active duty in the armed services, may also, under California law, grant a valid consent for hospital and medical care. However, once a minor is no longer on active duty, his ability to give consent to medical treatment terminates.

Persons less than 18, but more than 15 years of age who are living separate and apart from their parents or legal guardian, and who are managing their own financial affairs (regardless of the

source of income), are capable of granting legal consent to the rendition of medical services. Persons less than 18 years old but more than 12 may give consent to the furnishing of hospital, medical, and surgical care related to the diagnosis or treatment of any contagious or communicable disease, that is required by law to be reported to the local health offices.

In summary, AB 2887 enables persons 18 years old or older to give valid and legal consent to the rendition of medical care and treatment in the State of California. All other aspects of California law will remain the same with respect to the consent necessary before a physician can render medical care and treatment.

Because of the changes which have occurred in California with respect to the medical treatment of minors since December of 1970, a revised table, setting forth in summary form the legal consent requirements for medical treatment of minors is published on the opposite page. It should be used in place of the one published in December of 1970.

Legal Consent Requirements for Medical Treatment of Minors in Various Circumstances

<i>If Patient is</i>	<i>Is Parental Consent Required?</i>	<i>Are Parents Responsible For Cost?</i>	<i>Is Minor's Consent Required?</i>	<i>May M.D. Inform Parents of Treatment?</i>
Under 18, unmarried, no special circumstances	Yes	Yes	No	Yes
Under 18, married or previously married	No	No	Yes	No
Under 18, emergency and parents not available	No	Yes	Yes (If Capable)	Yes
Emancipated (over 15, not living at home, manages own financial affairs)	No	No	Yes	Yes
Unmarried, pregnant, under 18 (care related to pregnancy) (including consent to an abortion)	No	No	Yes	No
Unmarried, pregnant, under 18 (care <i>not</i> related to pregnancy and no other special circumstances)	Yes	Yes	No	Yes
Unmarried, under 18, determination if pregnant, no other special circumstances	Probably not	Probably not	Probably yes	Probably not
Under 18, on active duty with Armed Services	No	No	Yes	No
Under 18, over 12, care for contagious reportable disease	No	No	Yes	No
Birth control, under 18:				
Married or previously married	No	No	Yes	No
Emancipated	No	No	Yes	No
Care related to treatment of pregnancy	No	No	Yes	No
Not married or previously married, not emancipated, care not related to treatment of pregnancy	Yes	Yes	No	Yes

Clinical Note

Abraham Lincoln and Aortic Insufficiency

The Declining Health of the President

HAROLD SCHWARTZ, M.D., *Lynwood*

ACCORDING TO MANY OBSERVERS and subsequent scholars, the health of Abraham Lincoln in his last year of life was such as to preclude completion of his second term of office even if he had not been assassinated. Understandably, in the absence of a known organic basis for that unfavorable prognosis, the decline in the physical well-being of the President has been attributed to emotional factors attendant upon the burdens of office and a tragic war—an impression that only positive evidence, the subject of this report, can perhaps obviate.

Background and Hypothesis

Several years ago a case of the Marfan syndrome in a young boy under my care was presented and a pedigree given indicating his descent from Mordecai Lincoln II, a great-great grandfather of Abraham Lincoln.¹ Descriptive and genetic evidence was also submitted demonstrating that the striking morphologic characteristics of the 16th president were likewise those of the Marfan syndrome as derived from the ancestor held in common with the patient reported. While in the original communication only involvement of the skeletal and visual apparatus was documented for the President, material by which to infer in his case a cardiovascular lesion typical of arachnodactyly has long been available. Before this observation was reported, however, it was felt desirable, because of the indirect

nature of the data, to find a way to make this impression objective, and only recently has a method of accomplishing this been found. Evidence is therefore now offered suggesting that President Lincoln, two years before his assassination, had physical findings consistent with aortic insufficiency, as a complication of the Marfan syndrome.

The Evidence

The evidence suggesting a cardiovascular lesion in Abraham Lincoln actually evolves from certain observations and remarks of the president himself, together with those of Noah Brooks, a newspaperman, as they reviewed a photograph for which Mr. Lincoln had posed a short time previously^{2,3} (Figure 1). In the episode, as reported by Hamilton and Ostendorf,² the president was speaking:

"I can understand why that foot should be so enormous," he said to Brooks—"It's a big foot anyway, and it is near the focus of the instrument. But why is the outline of it so indistinct and blurred? I am confident I did not move it."

Brooks suggested that the throbbing of the arteries may have caused an imperceptible motion.

The President crossed his legs and watched his foot. "That's it! That's it!" he exclaimed. "Now that's very curious, isn't it?"³

Aortic insufficiency (AI) being a common lesion in the Marfan syndrome, the clinician will recognize in the suspended throbbing and pul-

From the Department of Medicine, University of Southern California School of Medicine, Los Angeles.

Submitted February 25, 1972.

Reprint requests to: H. Schwartz, M.D., 3633 East Century Blvd., Lynwood, Ca. 90262.



Figure 1.—The Photo-Kymographic Evidence: Lincoln noted that the outline of his left boot was blurred, and Brooks expounded upon the theory that the throbbing arteries caused the leg to move almost imperceptibly.³

sating foot of the President, a phenomenon entirely compatible with the hemodynamic effects of aortic regurgitation.

Fundamentally, such visible pulsations result from sudden filling of the large collapsed arteries accompanying aortic regurgitation. Corrigan in 1832 described this effect in the carotid, temporal and other like vessels while similar pulsations have since been described in the uvula, the liver and the capillaries. Even more applicable, cardiologist Luisada emphasizes, as a manifestation of the "vascular dance" accompanying AI, the abrupt "rhythmic extension of one leg when crossed over the other coincident with systole."⁴ Further, the eminent Sir Thomas Lewis states specifically that the jerking water-hammer quality of the pulse-wave of aortic incompetence "is extreme in the dorsum of the foot."⁵

Other studies reveal that in AI, the blood pressure in the femoral artery is greatly exaggerated over that of the brachial and since the femoral artery is in a direct line with the aortic stream while the brachial issues from the aorta at a right angle, the femoral receives both the pressure and the very considerable velocity head of the aortic

stream. This increased pressure and velocity head is precisely the mechanism that may produce pulsatile motion in a suspended leg and foot in AI, a lesion that in the Marfan syndrome is the direct result pathologically of dilatation of the aortic ring or myxomatous change of the aortic valve.

Independent objectifying evidence supporting the plausibility of the hypothesis offered is available in an analogous situation recently documented by a young journalist who himself had the Marfan syndrome. This man, in a recent book describing his personal medical experiences with ectopia lentis, loose-jointedness and aortic insufficiency, noted most perceptively:

"My heart had its work cut out . . . There was no need to feel my pulse. Its heavings were all too readily discernible in my neck, at my wrist and even on the back of my hand. And when I crossed my legs and let my muscles relax, the upper leg jumped up and down like a spring, keeping perfect rhythm with the beat of my heart muscle."⁶

That a non-physician with the same condition that affected Abraham Lincoln made this observation in himself, would appear to lend considerable reliability and validity to the similar observation and analysis made a hundred years previously by the laymen Lincoln and Brooks.

The pulsating suspended leg and foot phenomenon, which may be called the Lincoln-Brooks sign of aortic insufficiency, is made possible by the hinge-like arrangement of the related body parts. From this arises the possibility that laxness with hypertensibility of the joints, as commonly seen in arachnodactyly, may facilitate pulsatile motion of a suspended extremity even in the presence of lesser degrees of regurgitation than otherwise required for this phenomenon in cases of aortic insufficiency without hyperextensibility. While Lincoln was many times described by his contemporaries as "loose-jointed," further evidence specifically for the laxness of his ankle joint which may have made his foot, in addition to his leg, more responsive to minor degrees of regurgitation, is found in a description by Lincoln's law associate William Henry Herndon: "In walking, Mr. Lincoln put the whole foot flat down on the ground at once, not landing on the heel. He lifted his foot all at once—not lifting himself from the toes and hence had no spring or snap . . . to his . . . walk."⁷

While undoubtedly a mere coincidence, the fact remains that the pose assumed for the photograph under consideration, had Lincoln's lower extremities crossed, with the overhanging foot close to the lens where its arc, increased first by the rhythmically extended leg and then by the still oncoming steep pulse-wave reaching the foot, was optimal for producing "photokymographic" documentation of the President's "altered" circulatory dynamics.

As to other findings in aortic insufficiency, no blood pressure apparatus was clinically available in Lincoln's time by which to establish that there was a wide pulse-pressure. Regarding also the usual aortic diastolic decrescendo murmur: it may in any given case be absent or extremely difficult to elicit or localize, particularly in the presence of an altered configuration of the chest. Significantly, Mr. Lincoln has been shown¹ to have, as a skeletal component of the Marfan syndrome, a pectus excavatum which shifts the heart well into the left hemithorax, thereby rendering many of the cardiac findings less than typical. Furthermore, when detected, this murmur reflects diagnostically only the same pathologic condition that produces a bounding pulse, and in that sense the murmur is only one of many cardiovascular signs of aortic incompetence. The absence therefore of evidence for a diastolic aortic murmur in the President does not detract from the present diagnostic impression.

Discussion

Considering, then, the presence of the Marfan syndrome as previously established in Mr. Lincoln; the frequency of aortic valvular incompetency in that condition; the hemo-dynamics of aortic regurgitation; the graphic data of the Gardner photograph as detected by the President himself; the hypothesis of Brooks and its clinical confirmation by Lincoln; the leg and foot signs in the medical literature; the analogous clinical findings by a non-physician with arachnodactyly and the diagnostic criteria quoted, the evidence in the case of the President becomes highly consistent with aortic insufficiency and regurgitation.

Adding a cardiovascular lesion consistent with

arachnodactyly to the previously documented skeletal and visual findings in the case of the President reinforces considerably the original diagnosis of the Marfan syndrome as already authoritatively accepted elsewhere⁸ by completing involvement in all three major body systems any one or more of which may participate in the total spectrum of arachnodactyly as a heritable disorder of connective tissue.

Further, from the perspective of the present diagnostic impression, the course of the declining health of the President can be shown to be consistent with the late slow form of cardiac decompensation highly characteristic of AI. In relation to this, the period preceding Mr. Lincoln's violent death was one of easing burdens, lessening anxiety and lightening of spirit as the War Between the States drew to its long-awaited close. The health of the President, however, continued to deteriorate ever more rapidly, a paradox inconsistent with psychic stress as the one responsible factor. More compatible with the physical decline of Mr. Lincoln is a progressive decrease in cardiac reserve subsequent to long-standing aortic insufficiency, the course of which was abruptly terminated by his assassination on April 14, 1865.

In conclusion, if the diagnosis of the Marfan syndrome has resolved to any extent some of the enigma long surrounding President Lincoln, it also highlights one of the foremost problems of the genetic era—genetic control. As expressed by one authority citing by way of example the Marfan syndrome and Abraham Lincoln: ". . . who would dare wish him eugenically suppressed?"⁹

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Information

Gallop Rhythm

ROBERT A. O'ROURKE, M.D.

*Material Supplied by the American
Heart Association*

THE TERM "GALLOP RHYTHM" was originated by Professor Bouillaud and propagated by his pupil Potain more than a century ago. However, even today, the majority of gallop sounds are unrecognized or misinterpreted. This is unfortunate because gallop rhythm is frequently the only positive physical finding in patients with heart disease and its presence often has important diagnostic and therapeutic implications.

Gallop rhythm is an auscultatory phenomenon in which a tripling or quadrupling of heart sounds resembles the canter of a horse. Tachycardia need not be present. Gallop sounds are low frequency diastolic events related to two periods of ventricular filling: the rapid filling phase (third heart sound, ventricular gallop) and the presystolic filling associated with atrial systole (fourth heart sound, atrial gallop). Both third and fourth heart sounds may be present in the same patient. During tachycardia or advanced first degree A-v block, both gallop sounds may occur at almost the identical time, producing a summation gallop. The summation gallop may be confused with the diastolic rumble of mitral stenosis. However, decreasing the heart rate by transient carotid sinus pressure will separate the two gallops and distinguish them from a diastolic rumble.

Fourth Heart Sound

The fourth heart sound (presystolic gallop, atrial gallop) is a low frequency sound produced in the ventricle during the ventricular filling as-

sociated with an effective atrial contraction. The atrial gallop is occasionally heard in patients with no evidence of heart disease, particularly during times of high cardiac output such as occur with thyrotoxicosis or pregnancy. This presystolic sound is also heard in patients with first degree atrioventricular block (prolonged P-R interval on electrocardiogram). However, an audible fourth heart sound usually indicates heart disease and its presence is usually dependent on three factors: (1) effective atrial contraction, (2) unimpeded ventricular filling, and (3) diminished ventricular distensibility (stiff ventricle).

The fourth heart sound is never present in patients with atrial fibrillation and is an uncommon finding in patients with diminished left ventricular filling due to moderate or severe mitral stenosis. It is usually absent in patients with constrictive pericarditis. The atrial gallop generally signifies reduced ventricular distensibility and is frequently but not always associated with an increase in ventricular end-diastolic pressure.

The presystolic gallop may originate in the right or left ventricle. Left-sided fourth heart sounds are commonly present in patients with diastolic hypertension, severe aortic stenosis, myocardiopathies and acute mitral regurgitation. Most patients with an acute myocardial infarction and sinus rhythm have a prominent fourth heart sound. A presystolic gallop is a frequent finding in patients with coronary artery disease but may be only heard during an episode of angina.

Left-sided fourth heart sounds are frequently accompanied by visible palpable presystolic distension of the left ventricular apex. This is best observed with the patient on his left side. On phonocardiogram, the low frequency vibrations of the atrial gallop are coincident with the presystolic "a" wave of the apexcardiogram. The left-sided fourth heart sound is best heard by using light pressure with the bell of the stethoscope and is maximal in intensity at the left ventricular apex with the patient in the left lateral position. If patients are not turned to this position during auscultation, over 50 percent of atrial gallops will be undetected. The left-sided presystolic gallop is usually most prominent during the expiratory phase of respiration.

The atrial gallop increases in intensity and the fourth heart sound-first heart sound interval

Dr. O'Rourke is from the Department of Medicine, University of California, San Diego, School of Medicine.

lengthens as the result of an increase in ventricular filling, a prolongation of atrioventricular conduction or a decrease in ventricular distensibility. During bedside auscultation the left-sided atrial gallop is usually accentuated after coughing and during mild supine exercise. It also becomes prominent during a sustained handgrip contraction. During these maneuvers the fourth heart sound-first heart interval frequently increases in contrast to splitting of the first heart sound which becomes less evident with the increase in heart rate.

Right-sided fourth heart sounds are frequently present in patients with right ventricular hypertrophy secondary to either pulmonary hypertension or pulmonary stenosis. They are commonly accompanied by a prominent presystolic "a" wave in the jugular venous pulse and a parasternal or subxiphoid right ventricular lift. These low frequency sounds are heard best at the third to fifth left intercostal spaces and often increase in intensity during inspiration.

Both the right- and left-sided fourth heart sounds can often be distinguished from the two components of the first heart sound by applying increasing chest wall pressure with the bell piece of the stethoscope. As pressure is increased the bell functions as a diaphragm and low frequency sounds such as the fourth heart sound usually decrease in intensity or disappear. In contrast, the high frequency components of the first heart sound persist unchanged.

Third Heart Sound

The third heart sound (ventricular gallop, proto diastolic gallop) is a low frequency sound produced in the ventricle in early diastole during passive rapid filling. This early diastolic sound is a frequent finding in normal children and young adults and also in patients with a high cardiac output. However, the presence of a third heart sound in patients over the age of 40 generally indicates ventricular decompensation or A-v valve regurgitation. The ventricular gallop, like the fourth heart sound, can be produced in either ventricle and is heard best with the bell piece of the stethoscope. The left-sided third heart sound, commonly present in patients with left heart failure or mitral regurgitation, is heard best on the left ventricular apex with the patient in the left lateral position. This low fre-

quency sound is most prominent during expiration. The right-sided ventricular gallop, frequently present in patients with right heart failure or tricuspid regurgitation, is heard best at the lower left sternal border and increases with inspiration. It is often accompanied by a prominent late systolic "v" wave in the jugular venous pulse, the systolic murmur of tricuspid regurgitation, and a large liver which pulsates in late systole. The third heart sound occurs later in diastole than the higher frequency A-v valve opening snap from which it must be distinguished. The ventricular gallop, unlike the opening snap, decreases or disappears when the patient assumes the upright position.

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In Memoriam

BRODKIN, MICHAEL F., Beverly Hills. Died March 11, 1972 in Santa Monica of heart disease, aged 61. Graduate of the University of Illinois College of Medicine, Chicago, 1935. Licensed in California in 1941. Doctor Brod-kin was a member of the Los Angeles County Medical Association.

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COLLINS, VERNON, Pacoima. Died November 23, 1971, aged 75. Graduate of Howard University College of Medicine, Washington, 1923. Licensed in California in 1958. Doctor Collins was a member of the Los Angeles County Medical Association.

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COOPER, CHARLES LANDRY, Los Angeles. Died Febru-ary 18, 1972 in Los Angeles, aged 61. Graduate of the University of Tennessee College of Medicine, Memphis, 1932. Licensed in California in 1933. Doctor Cooper was a member of the Los Angeles County Medical As-sociation.

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DAWSON, EARL M., Los Angeles. Died March 16, 1972 in Glendale of heart disease, aged 71. Graduate of Col-lege of Osteopathic Physicians and Surgeons, Los An-geles, 1948. Licensed in California in 1948. M.D. de-gree from California College of Medicine, 1962. Doctor Dawson was a member of the Los Angeles County Medi-cal Association.

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FONG, EVAN, Sacramento. Died March 11, 1972 of heart disease, aged 48. Graduate of the College of Med-ical Evangelists, Loma Linda-Los Angeles, 1948. Licensed in California in 1948. Doctor Fong was a member of the Sacramento County Medical Society.

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GALLANT, ALFRED EDWARD, Los Angeles. Died Febru-ary 27, 1972 in Los Angeles of acute pancreatitis, aged 88. Graduate of Tufts College Medical School, Boston, 1916. Licensed in California in 1917. Doctor Gallant was a member of the Los Angeles County Medical Association.

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KARGANILLA, NARCISCO AQUINO, Newhall. Died Sep-tember 28, 1971 in Los Angeles, aged 44. Graduate of the University of the Philippines College of Medicine, Manila, 1953. Licensed in California in 1969. Doctor Karganilla was a member of the Los Angeles County Medical Association.

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KEGEL, ARNOLD HENRY, Los Angeles. Died March 1, 1972 in Beverly Hills of coronary artery disease, aged 76. Graduate of the Loyola University School of Medicine, Chicago, 1916. Licensed in California in 1936. Doctor Kegel was a member of the Los Angeles County Medical Association.

KOOTSEY, JOSEPH STEVEN, San Jose. Died March 14, 1972 in San Jose, aged 66. Graduate of the College of Medical Evangelists, Loma Linda-Los Angeles, 1933. Li-censed in California in 1952. Doctor Kootsey was a member of the Santa Clara County Medical Society.

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NEWTON, HIRAM D., San Diego. Died March 11, 1972, aged 73. Graduate of the University of Kansas School of Medicine, Lawrence-Kansas City, 1925. Licensed in California in 1928. Doctor Newton was a retired mem-ber of the San Diego County Medical Society and the California Medical Association, and an associate member of the American Medical Association.

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PRENTISS, ROBERT J., San Diego. Died March 8, 1972 in San Diego, aged 62. Graduate of State University of Iowa, College of Medicine, Iowa City, 1934. Licensed in California in 1942. Doctor Prentiss was a retired mem-ber of the San Diego County Medical Society and the California Medical Association, and an associate member of the American Medical Association.

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SEECH, STEPHEN G., Los Angeles. Died February 2, 1972 in Los Angeles of heart disease, aged 74. Gradu-ate of Magyar Királyi Pázmány Péter Tudományegyetem Orvosi Fakultása, Budapest, 1921. Licensed in Califor-nia in 1925. Doctor Seech was a member of the Los Angeles County Medical Association.

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SOSSON, EDWARD, San Bernardino. Died March 15, 1972 in San Bernardino, aged 59. Graduate of the Uni-versity of Illinois College of Medicine, Chicago, 1938. Licensed in California in 1946. Doctor Sosson was a member of the San Bernardino County Medical Society.

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STEVENS, JOSEPH B., Los Angeles. Died January 14, 1972, aged 76. Graduate of the University of Illinois College of Medicine, Chicago, 1920. Licensed in Cali-fornia in 1925. Doctor Stevens was a member of the Los Angeles County Medical Association.

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TIMME, ARTHUR R., Los Angeles. Died March 20, 1972 in Altadena of heart disease, aged 81. Graduate of Case Western Reserve University School of Medicine, Cleveland, 1915. Licensed in California in 1919. Doctor Timme was a member of the Los Angeles County Medi-cal Association.

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WALLEY, ORVAL JOSEPH, Long Beach. Died February 28, 1972 in Long Beach of heart disease, aged 62. Gradu-ate of Ohio State University College of Medicine, Col-umbus, 1942. Licensed in California in 1943. Doctor Walley was a member of the Los Angeles County Medi-cal Association.



Acid Secretion and Serum Gastrin Levels In the Zollinger-Ellison Syndrome

R. EDWARD SANCHEZ, M.D., WILLIAM P. LONGMIRE, JR., M.D., AND
EDWARD PASSARO, JR., M.D., Los Angeles

■ *Thirteen cases of patients with the Zollinger-Ellison syndrome were reviewed. In two cases the diagnosis was made by incidental biopsy of small liver nodules at operation for peptic ulcer disease.*

Seven patients had gastric secretory tests which showed a basal acid output to maximum acid output ratio of more than 65 percent. Five patients had BAO:MAO ratios less than 50 percent.

A 30-month interval between incidental discovery of tumor and clinically evident disease was observed in two patients. Recurrence of symptoms after excision of tumor was noted after a similar interval in another case.

Serum gastrin levels, before total gastrectomy, were elevated in all cases. The lowest preoperative level in this series of patients was 550 picograms per ml (normal 100 to 150 picograms). They were diagnostic in two patients with normal gastric secretory studies. The levels fell to normal following total gastrectomy in six patients. Two patients still had elevated levels five years and 14 years after total gastrectomy. One was discovered to have a parathyroid adenoma with hypercalcemia.

Total gastrectomy was curative in all the patients with the Zollinger-Ellison syndrome; lesser operations were not.

ESTABLISHING THE DIAGNOSIS OF THE Zollinger-Ellison syndrome may require exhaustive study

From the Department of Surgery, Veterans Administration Hospital (Wadsworth), and the Department of Surgery, University of California, Los Angeles, School of Medicine.

Submitted April 12, 1971.

Reprint requests to: E. Passaro, Jr., M.D., Department of Surgery, Veterans Administration Center, Wilshire and Sawtelle Boulevards, Los Angeles, Ca. 90073.

of the patient over many years. A persistent ulcer diathesis and gastric hypersecretion are usually the first clues in the diagnosis.¹ Typically, patients have pronounced elevation of basal acid secretion. The ratio of basal acid output to maximum acid output (BAO:MAO) is usually greater than 65 percent.^{2,3}

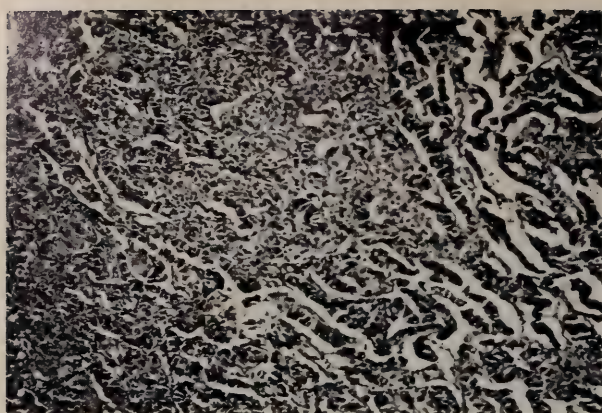


Figure 1.—Photomicrograph of liver nodule (Case 1) showing metastatic islet cell carcinoma. (Magnification X400. Hematoxylin-eosin stain.)

This report is based on data obtained from an extensive study of 13 patients with the Zollinger-Ellison syndrome. The patients were carefully followed by serial gastric secretory tests, by serum gastrin determinations, and, in two cases, by coeliac angiography. The case histories illustrate the difficulty in establishing the diagnosis by previously described methods and establish the value of serum gastrin determinations.

Reports of Cases

Case 1. A 43-year-old Caucasian man was seen for elective repair of an incisional hernia. Two years previously, he had had vagotomy and pyloroplasty for a bleeding duodenal ulcer. On biopsy at that time a nodule in the left lobe of the liver was thought to be a metastatic "papillary carcinoma." The postoperative course was complicated by infection and uremia requiring peritoneal dialysis and wound dehiscence. The biopsy slides (Figure 1) were reviewed and a diagnosis of metastatic islet cell carcinoma was made. Gastric secretory tests (Table 1, a) were within normal limits. A ventral hernia was repaired, the abdomen explored, and no tumor found. Ulcer symptoms continued and gastric secretory tests two years later showed decidedly elevated levels (Table 1, b). At operation there were large metastatic deposits within the liver and the region of the coeliac axis. A total gastrectomy* with Roux-en-Y esophagojejunostomy was done. The patient has done well and is working regularly as a machinist. His serum

*Total gastrectomy is 100 percent resection of stomach with histological evidence of circumferential esophageal mucosa at the proximal margin of the specimen and circumferential duodenal mucosa at the distal margin.

TABLE 1.—Gastric Secretory Studies on 12 Patients with the Zollinger-Ellison Syndrome

Case	Anatomy*	Acid Secretion mEq per hour		
		Basal	Maximum**	BAO:MAO***
1 a	V & P	3	47	.06
b	V & P	56	80	
2 c	Normal	4	15	
d	B II	23	27	.85
e	B I	9	11	
3 f	Normal	8	33	.24
g	B I	29	45	
4 h	B II	0.6	1.6	.38
i	B II	3	12	
5 j	Normal	80	72	1.11
k	V & P	61	81	
l	V & P	18	61	
m	V & P	63	76	
6 n	B II	16	17	.94
o	B II	4	23	
7 p	Normal	30	42	.71
8 q	Normal	26	56	.46
r	Normal	21	60	
9 s	Normal	13	14	.92
10 t	Normal	37	77	.48
11 u	B II	4.1	4.6	.90
13 v	Normal	14.7	17.7	.83
w	V & P	12	40	

*ANATOMY—V & P: Vagotomy and pyloroplasty. BI: Hemigastrectomy with gastroduodenostomy (Billroth I). B II: Hemigastrectomy with gastrojejunostomy (Billroth II).

**Maximum gastric acid secretion following intramuscular injection of betazole hydrochloride (Histalog®, Eli Lilly)—1.5 mg/Kg. body weight.

***Basal acid output: maximum acid output at time of diagnosis.

gastrin level, three years after total gastrectomy, was 3 picograms per ml.

Case 2. A 50-year-old Negro man with a five-year history of duodenal ulcer and three previous episodes of bleeding requiring transfusion underwent emergency vagotomy and hemigastrectomy (Billroth II) in October, 1962. A gastric secretory study was normal (Table 1, c). The patient was well until 1965, when bleeding recurred. Basal gastric secretion was elevated (Table 1, d) and the Zollinger-Ellison syndrome was suspected. Despite extensive exploration, no tumor was found, and the previous anastomosis was converted to a gastroduodenostomy. He was well until October, 1968, when bleeding recurred. The serum gastrin level was found to be elevated (Table 2), establishing the diagnosis.

Case 3. A 45-year-old Negro man had intractable duodenal ulcer disease for 12 years. Gastric secretory levels were not extraordinary (Table 1, f). In September, 1965, vagotomy and

TABLE 2.—Serum Gastrin Levels in 13 Patients with the Zollinger-Ellison Syndrome

Case	Anatomy	Postoperative Time Interval	Serum Gastrin Picograms/Ml
1	Total gastrectomy	3 years	3
		5 years	5,000
2	Billroth I	4 months	600
3	Billroth I	3 years	7,000
	Total gastrectomy	2 months	3,333
4	Billroth II	3 months	550
5	Normal		2,000
	Total gastrectomy	7 months	87
6	98% gastrectomy	3 years	3,350
7	98% gastrectomy	3 years	2,000
8	Total gastrectomy	4 years	67
9	Total gastrectomy	14 months	4
10	Total gastrectomy	3 months	17
11	Billroth II	3 days	683
12	Total gastrectomy	14 years	6,600
	Preop parathyroid adenomectomy		8,000
	Parathyroid adenomectomy	1 week	10,000
13	Vagotomy and pyloroplasty	2 years	600

hemigastrectomy were done. A 5 mm pale yellow nodule on the right lobe of the liver was excised and diagnosed as a metastatic islet cell tumor (Figure 2). The pancreas and the duodenum were then carefully explored and no other tumors noted. The symptoms were relieved for a time but returned within a few months. Because of continued ulcer symptoms, the patient was readmitted in January, 1969. Serum gastrin levels were decidedly elevated (over 7,000 picograms per ml) as were the gastric acid levels (Table 1, g). At operation, a 7 cm tumor in the liver and a 4 cm tumor in the pancreas were found. Total gastrectomy with loop esophagojejunostomy and entero-enterostomy with intra-loop jejunal limb ligation was done.

Case 4. A 47-year-old Negro man was seen in September, 1965, with gastric retention from duodenal ulcer disease. On nasogastric tube drainage, the gastric output averaged three liters a day, with an acid concentration of 30 mEq per liter. A gastrin-secreting islet cell tumor was suspected and one was found embedded in the head of the pancreas. The tumor was removed and vagotomy and Billroth II resection were done. A postoperative acid study showed low levels (Table 1, h). The patient was admitted



Figure 2.—Photomicrograph of liver nodule (Case 3) showing metastatic islet cell carcinoma. (Hematoxylin-eosin stain.)

again in November, 1968, because of melena. The acid secretion had increased (Table 1, i). The serum gastrin level was elevated to 550 picograms per ml. Total gastrectomy with Roux-en-Y esophagojejunostomy was done in March, 1969.

Case 5. A 36-year-old Caucasian man was referred with a diagnosis of multiple endocrine adenoma and with complaints of diarrhea, weight loss, nausea, and vomiting of three years' duration. Preoperative studies revealed elevated serum calcium (12.7 mg per 100 ml) and serum gastrin (2,000 picograms per ml) levels, a non-functioning thyroid nodule, and a maximum basal acid secretion of 111 mEq per hour with an average basal secretion of 80 mEq per hour (Table 1, j). At operation in March, 1966, "tumors of the pancreas" and a right adrenal adenoma were removed. On permanent section, the "pancreatic tumors" were identified as metastatic islet cell adenocarcinoma in lymph nodes. The acid secretion was unchanged by operation (Table 1, k). In April, 1966, the patient had right hemithyroidectomy and right inferior parathyroidectomy for adenomata. Basal acid secretion fell to 18 mEq per hour (Table 1, l) and the patient became asymptomatic. Diarrhea, nausea and vomiting recurred two and a half years later. Basal acid secretion had increased to 63 mEq per hour (Table 1, m). Total gastrectomy with Roux-en-Y esophagojejunostomy was done in September, 1968. The serum gastrin level was 87 picograms per ml five months after operation.

Case 6. A 53-year-old Negro man was seen first in November, 1952, with a three-day history

of pain and vomiting. In the next 18 months he was re-admitted four additional times for similar complaints. A duodenal ulcer niche was seen on several x-ray studies of the upper gastrointestinal tract. Antrectomy and vagotomy were done in June, 1954, for intractability and bleeding. During the next eight and a half years the patient was admitted to hospital 18 times for marginal or jejunal ulcers, bleeding, pain, and vomiting. He refused operation. Basal acid secretion was 18 mEq per hour. In January, 1965, an abdominal exploration for a pancreatic tumor was made but none was found. Five days following operation the patient had an emergency resection to control bleeding associated with gastritis. A 2 cm cuff of stomach was left on the esophagus to insure adequate anastomosis.

Since operation, the patient has had two episodes of bleeding. An ulcer in the gastric remnant was demonstrated in November, 1967. A pH electrode passed down the esophagus demonstrated acid-secreting (pH 1) mucosa. The patient refuses further operation. His serum gastrin level is 3,350 picograms per ml.

Case 7. A 43-year-old Caucasian man was admitted to hospital in 1964 with a four-year history of abdominal pain. An upper gastrointestinal series showed duodenitis and pancreatic calcifications. High basal acid levels (Table 1, p) suggested the diagnosis of the Zollinger-Ellison syndrome. The patient was readmitted eight months later because of pain, nausea, vomiting and diarrhea. In July, 1965, a near total gastrectomy was done after the diagnosis of a metastatic nodule on the liver was confirmed by biopsy. The patient continued to have epigastric pain and weight loss. A serum gastrin level obtained three years after operation was 2,000 picograms per ml. A pH electrode passed down the esophagus confirmed the presence of acid-secreting (pH 1) mucosa. The patient died of metastatic disease and cachexia four years after operation.

Case 8. A 38-year-old Negro man was first seen in December, 1961, with a three-year history of ulcer symptoms relieved by antacids. The basal secretory acid level was 2.6 mEq per hour. The patient was admitted for evaluation of hypercalcemia (11.5 to 13.8 mg per 100 ml). An upper gastrointestinal series showed a deformed duodenal bulb without ulceration. Bilateral inferior parathyroidectomy was carried out for a left inferior parathyroid adenoma. The patient was re-

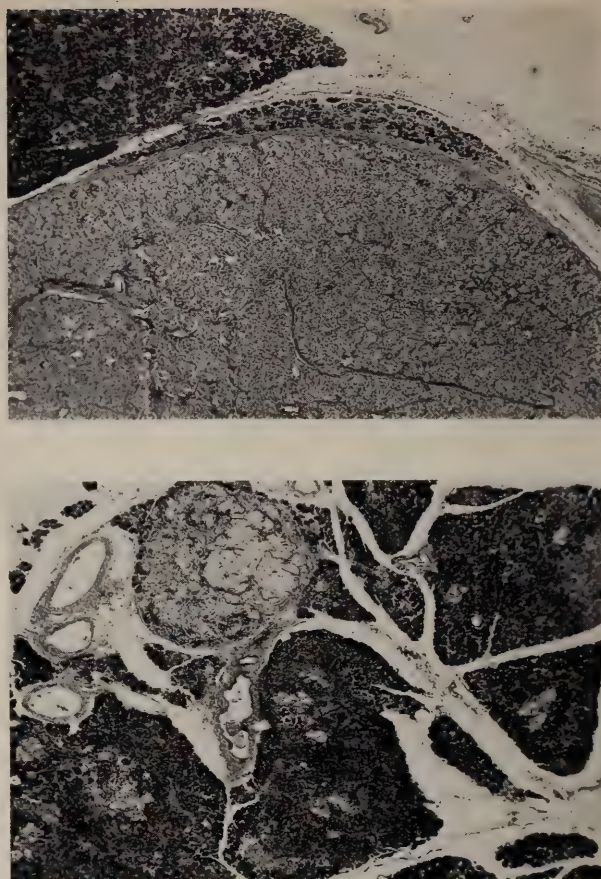


Figure 3.—Photomicrographs of pancreatic biopsy (Case 8) showing adenomatosis. (Magnification in upper frame, X25; in lower frame, X1000. Hematoxylin-eosin stain.)

admitted in April, 1965, with a history of melena and hematemesis, and found to have elevated acid levels (Table 1, q) and serum calcium levels (9.6 to 13 mg per 100 ml). A duodenal ulcer was visualized by x-ray studies. Partial pancreatectomy was carried out in May, 1965, for multiple adenomata (Figure 3). Postoperatively, acid levels remained elevated (Table 1, 4) and there was an episode of bleeding. A month later, total gastrectomy with esophagojejunostomy and entero-enterostomy was carried out. In October, 1969, the patient was discovered to have diabetes mellitus, easily controlled by diet and oral hypoglycemic agents. The serum gastrin level was 67 picograms per ml four years after total gastrectomy.

Case 9. A 65-year-old Caucasian woman with two-year history of epigastric pain, high BAO:MAO ratios (Table 1, s) and suspected Zollinger-Ellison syndrome, underwent operation for a posterior penetrating duodenal ulcer in March, 1969.

A 6 x 8 cm islet cell adenocarcinoma was found occupying the body and tail of the pancreas, and was removed by partial pancreatectomy. Total gastrectomy with Roux-en-Y esophagojejunostomy was performed at the same time. Postoperative pancreatic insufficiency was corrected by oral pancreatic enzyme supplementation. The serum gastrin level, 20 months after operation, was 4 picograms per ml. The patient gained 20 pounds in weight in the two years following operation.

Case 10. A 44-year-old Caucasian man with no previous history of ulcer disease underwent emergency operation for a perforated jejunal ulcer in August, 1968. An upper gastrointestinal x-ray series three months later revealed coarse mucosal folds in the duodenum, a deformed duodenal bulb, and evidence of retained secretions in the stomach. Gastric secretory studies were elevated (Table 1, t) but selective pancreatic arteriography was normal. Vagotomy and pyloroplasty were performed after thorough exploration of the abdomen, multiple biopsy and a partial pancreatectomy failed to reveal a tumor. The pancreas was nodular and firm but was normal on microscopic examination. Two months later, the patient returned with outlet obstruction and a gastric output of three liters daily with an acid concentration of 74 mEq per liter. After decompression, a large jejunal ulcer was seen on upper gastrointestinal series. Total gastrectomy with Roux-en-Y esophagojejunostomy was performed in February, 1969. No tumor was found. The stomach showed parietal cell hyperplasia. The serum gastrin level ten months after operation was 17 picograms per ml.

Case 11. A 38-year-old Caucasian woman with a one-month history of epigastric pain was discovered by x-ray studies to have gastric and duodenal ulcers. Multiple right renal stones and a large left renal stone were demonstrated by intravenous pyelography. A glucose tolerance test revealed diabetes mellitus. The ulcers healed with antacid therapy in one month. Four months later, in October, 1968, the patient had an emergency operation to close a perforated duodenal ulcer. In January, 1969, antrectomy, vagotomy and gastrojejunostomy were performed for bleeding gastritis. Bleeding recurred a month later, and an 80 percent gastrectomy was done. Exploration and biopsy of the pancreas revealed inflammatory changes only. The postoperative

course was complicated by bleeding, fever, jaundice, and myocardial infarction. Gastric secretory studies, performed for the first time, revealed a basal level of 4 mEq per hour (Table 1, u). A serum gastrin level of 683 picograms per ml established the diagnosis of Zollinger-Ellison syndrome. Total gastrectomy with Roux-en-Y esophagojejunostomy was done in October, 1969. A large pancreatic islet cell tumor with hepatic metastasis was found. The patient was well seven months after the operation.

Case 12. A 48-year-old Caucasian man who had peptic ulcer disease since 1944 had gastric resection in 1950 for intractable duodenal ulcer. Three years later, total gastrectomy was done for bleeding recurrent ulcers. He had no ulcer symptoms thereafter. In 1965, the patient's brother was found to have the Zollinger-Ellison syndrome, which prompted evaluation of the entire family. It was discovered that three of four brothers and one of four sisters had the syndrome. The patient's daughter was discovered to have three parathyroid adenomas and a pancreatic adenoma. She had severe diarrhea but no symptoms of peptic ulcer disease. In October, 1967, the patient's serum gastrin level was 6,600 picograms per ml. In October, 1969, he developed symptoms of hypercalcemia. Two parathyroid adenomas were removed and the serum calcium level returned to normal. Serum gastrin levels, obtained preoperatively and postoperatively, were 8,000 and 10,000 picograms per ml respectively.

Case 13. A 14-year-old Negro boy was admitted for surgical correction of a duodenal ulcer that had been present for one year and had been refractory to intensive medical treatment. The patient's symptoms were epigastric pain, vomiting, and weight loss. An upper gastrointestinal series showed a duodenal ulcer niche with coarse gastric and duodenal mucosal folds. Gastric secretory studies (Table 1, v) showed a basal acid output of 14.7 mEq per hour and a maximum stimulated output of 17.7 mEq per hour. A diagnosis of Zollinger-Ellison syndrome was made. At laparotomy, a 4 cm islet cell adenocarcinoma was removed from the head of the pancreas. Two duodenal ulcers were found and vagotomy and pyloroplasty were done.

The patient then was well for eight months before epigastric pain recurred. The pain was mild and infrequent and was relieved by milk. The patient noticed black stools on two occa-

sions. An upper gastrointestinal series showed the effects of the pyloroplasty, but no prominent folds or ulcer niche were identified. Gastric secretory studies (Table 1, w) revealed a basal acid output of 12 mEq per hour and a maximum stimulated acid output of 40 mEq per hour. The serum gastrin level was over 600 pg per ml.

Discussion

The value of repeated gastric secretory studies in patients with recurrent peptic ulcer disease is evident in the cases here reported. The test is simple and readily available. It is reported that most patients with the Zollinger-Ellison syndrome will have BAO:MAO ratio of 65 percent or more.^{2,3} A lower ratio, however, does not rule out the syndrome.⁴ In this series of 13 patients, five had ratios of less than 50 percent at the time of diagnosis and two of the five had metastatic disease. In most patients the basal acid secretory levels will be continuously elevated. One of our patients (Case 4) was an exception. He had basal acid levels less than 5 mEq per hour consistently for four years. These levels were obtained after the patient had had a hemigastrectomy, but at a time when he was symptomatic from a marginal ulcer. He initially presented with outlet obstruction and a high gastric output. Acid levels at this time were 30 mEq per liter. This led to the correct diagnosis. The tumor was located in the head of the pancreas at celiotomy. This illustrates the importance of serial gastric analysis for patients presenting with complications of duodenal ulcer disease.

Two patients (Cases 1 and 3) were diagnosed by biopsy of small "incidental" tumor nodules on the liver at operation for duodenal ulcer. In these patients results of secretory studies were normal and there were no historical data suggesting the Zollinger-Ellison syndrome. One patient had a mistaken diagnosis of "papillary carcinoma" when the islet cell origin of the biopsy specimen was not recognized. He later presented for elective ventral hernia repair. After review of the biopsy slides, the abdomen was thoroughly explored at incisional herniorrhaphy. Additional tumor was not found. The patient continued with symptoms of duodenal ulcer and finally showed elevated acid levels. The other patient underwent operation for intractable duodenal ulcer disease. A 5 mm nodule was removed from



Figure 4.—Celiac arteriogram demonstrating metastatic islet cell tumor in the celiac axis (upper arrow) and jejunal mesentery (lower arrow) confirmed by laparotomy.

the liver and it proved to be metastatic islet cell adenocarcinoma. Three years later, the secretory studies became characteristically elevated.

The period between fortuitous discovery of tumor and onset of hypersecretion was two and a half years in three patients. Symptoms recurred in one patient (Case 5) after removal of multiple adenomata including metastatic islet cell tumors to peripancreatic lymph nodes. Operation revealed metastatic deposits in the coeliac axis and jejunal mesentery which had been demonstrated preoperatively by coeliac angiography (Figure 4). Hypersecretion was noted two and a half years after incidental discovery of tumor in the other two patients (Cases 1 and 3).

Two patients (Cases 5 and 8) presented with multiple adenomata and hyperparathyroidism. The combination of hypercalcemia and peptic ulcer disease suggests multiple endocrine adenomata.⁵ The patients had serum calcium levels of 12.7 and 13.8 mg per 100 ml, and both had history of duodenal ulcer disease. One had a basal acid output of 111 mEq per hour and adenomata in the pancreas, adrenal, thyroid and parathyroid glands. The other had normal secretory studies and a functioning parathyroid adenoma. Three years later, the latter had basal acid output of 26 mEq per hour, and multiple adenomata were found in the pancreas. Only by repeated secretory studies was the correct diagnosis reached. Patients with hypercalcemia and peptic ulcer disease should have serum gastrin determinations.

Serum gastrin levels, measured by a radioimmunoassay technique, were determined in all

patients (Table 2).^{*} In contrast to gastric secretory studies, serum gastrin levels were elevated in all patients before total gastrectomy. Gastrin levels may be diagnostic at a time when acid studies are normal (Cases 1 and 3). The test should be performed on all patients suspected of having this syndrome.

A drop in the serum gastrin level was noted in six patients following total gastrectomy. Two patients (Cases 6 and 7) who had near-total gastrectomy, as well as all other patients undergoing less than total gastrectomy, continued to have diagnostically elevated serum gastrin levels and clinically evident disease.

Two patients (Cases 1 and 12) with total gastrectomy had elevated serum gastrin levels five years and 14 years after the operation. Both patients were asymptomatic. The second patient

^{*}The serum gastrin determinations were performed by Dr. James E. McGuigan (Cases 4 to 10) and Dr. Rosalyn Yalow (Cases 1 to 3, 11 to 13).

was found to have a parathyroid adenoma with hypercalcemia. The serum gastrin remained elevated following removal of the adenoma and return to normal serum calcium levels.

Total gastrectomy was curative in all cases. None of these patients was cured of the disease by a lesser operation. As long as acid-producing parietal cells and gastrin-producing tumor cells are present, the disease continues. Frozen section documentation of total gastrectomy at celiotomy is imperative.

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Systemic Candidiasis, A Diagnostic Challenge

JAMES M. HUGHES, M.D., AND JACK S. REMINGTON, M.D., *Stanford*

■ *The serious and increasing problem of deep-seated Candida infection and the difficulties encountered in diagnosis of this entity prompted review of all well-documented cases of systemic candidiasis in a 39-month period at Stanford Medical Center. In only 19 of the 40 cases (47.5 percent) was the diagnosis suspected premortem; in 15 (37.5 percent) of these, the diagnosis was established. Thirty-three (82.5 percent) of the 40 patients died, and in 12 (39.4 percent) of them Candida infection was considered to be the primary cause of death or a major contributing factor. The seven survivors were treated either by specific chemotherapy or drainage of abscesses and empyema cavities. When the data were assessed in relation to underlying diseases and other possible predisposing factors, surgery was implicated in 50 percent of the total. In a study to define the prevalence of Candida in the saliva of patients with severe underlying illnesses receiving antibiotics or immunosuppressive therapy at the Stanford Medical Center, a significantly higher prevalence was noted in the multiple therapeutic modality group than in controls.*

In a review of reported data on methods for serological diagnosis of systemic candidiasis, only the precipitin and agglutinin methods appear promising.

SYSTEMIC FUNGAL DISEASES have become increasingly prevalent in recent years.^{1,2} By far the most common etiological agents have been members of the genus *Candida*.¹⁻⁸ These infections characteristically occur in patients (1) with severe underlying diseases, (2) receiving antibiotic, adrenal glucocorticoid, cytotoxic drug or radiation therapy, (3) with diabetes, (4) with indwelling intravenous catheters, or (5) following surgical operation.¹⁻¹⁰ The mechanisms by which

antibiotics, glucocorticoids, cytotoxic agents, and diabetes might predispose to fungus infections have been reviewed extensively elsewhere.^{2,9,11-14}

In spite of increasing awareness of the settings in which *Candida* infections occur, the majority are still diagnosed only at autopsy. For example, only 30 percent of 71 acute leukemics with systemic candidiasis studied by Bodey,¹ 14 percent of 14 renal transplant patients with systemic candidiasis studied by Rifkind et al,⁴ and 17 percent of 23 acute leukemics with systemic candidiasis studied by Preisler et al¹⁵ was the condition diagnosed premortem. Taschdjian et al obtained positive premortem blood cultures from only 7 of their 17 cases of disseminated candidiasis,¹⁶ and

From Stanford University School of Medicine (Hughes), Palo Alto Medical Research Foundation, and the Division of Infectious Diseases, Stanford University School of Medicine (Remington).

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Reprint requests to: J. S. Remington, M.D., Chief, Allergy, Immunology and Infectious Diseases Division, Palo Alto Medical Research Foundation, 860 Bryant Street, Palo Alto, Ca. 94301.

only 7 of the 42 cases reported by Hart et al² were diagnosed early enough that therapy could be initiated premortem.

The serious and increasing problem of deep-seated *Candida* infection and the difficulties encountered in diagnosis of this entity prompted the present study, the purpose of which was threefold. First, data in all well documented cases of systemic candidiasis occurring during the past three years at Stanford University Hospital and the Palo Alto Veterans Administration Hospital were reviewed to define the problem as it now exists. Second, the prevalence of *Candida* in the saliva of patients with various diseases and on different therapeutic regimens was determined and compared with control groups. Third, methods of diagnosing systemic candidiasis antemortem were reviewed to gain a better understanding of available methods and their limitations.

Materials and Methods

Bacteriology, surgical pathology, autopsy, and medical records from July 1, 1967, to September 30, 1970 were reviewed at the Stanford University and Palo Alto Veterans Administration Hospitals. The criteria for systemic infection were histological identification of *Candida* organisms in tissue other than skin or mucosal surfaces, positive culture from abscess or cerebrospinal fluid, or two or more positive blood cultures obtained on different days. Four cases with positive blood cultures associated with a positive culture of an intravenous catheter tip and no histological evidence of *Candida* at postmortem were not included. Cases in which positive cultures of internal organs for *Candida* were obtained postmortem in the absence of histological demonstration of the fungus were also not included. Finally, cases from the second half of 1967 previously reported by Hart et al² were eliminated.

Surgical operation was considered a predisposing factor if it occurred during the same time in hospital that the diagnosis of systemic candidiasis was made. Steroids, cytotoxic drugs, and antibiotics were considered if they were administered on at least 2 of the 28 days before the diagnosis, and radiotherapy was considered if it had been administered within the previous year. Since it was not possible to decide in all cases if patients had intravenous catheters in place just

before or at the time of diagnosis, this category was omitted. *Candida* infection was considered to have been suspected only if it was specifically stated in the patient's chart. Isolation of *Candida* from the oral cavity and sputum, urine, and surgical wounds was not considered as diagnostic of deep infection. It was not always possible to determine if the *Candida* infection was the primary cause of death, and in these cases it was considered a contributing cause. Concomitant bacterial or other fungus infections in these patients were not further considered but are indicated in Table 1.

Specimens of saliva were obtained in sterile plastic containers from 119 inpatients and outpatients at Stanford University Hospital and from 30 healthy controls, consisting primarily of medical students and laboratory personnel. Drug histories were obtained from all patients and controls, and individuals were placed in groups determined by whether or not they had received antibiotics, glucocorticoids, cytotoxic agents, head and neck radiation therapy, or a combination within the previous four weeks. The procedure used for identification of fungi in the saliva was the same as that employed by the Infectious Disease Laboratory at Stanford University Hospital. Specimens were plated in duplicate on Sabouraud's dextrose agar (Difco) and mycobiologic agar (Difco) and incubated at 23° C and 37° C for four weeks. Nonbacterial colonies were subcultured on Levine's EMB agar (Difco), and *Candida albicans* was identified by typical chlamydospore formation. Other species of *Candida* were not further identified.

Results

Cases of deep fungal infection

The 40 cases of documented deep fungal infection collected from the 39-month study period are summarized in Table 1. The series included 22 males and 18 females, and, after eliminating the 10 cases in males from the Veterans Administration Hospital, the female cases predominated, contrary to the findings of Hart et al² and Rifkind et al.⁴ Thirty-seven of the 40 patients had received antibiotics during the four weeks before diagnosis, 19 of 39 had received adrenal glucocorticoids,* 11 of 40 had received cytotoxic drugs, and only 1 of 40 had received radiotherapy. Twenty-two of the 40 had had surgical operation

*In one patient, this could not be determined from data at hand.

TABLE 1.—Data in 40 Cases of Systemic Candidiasis (1967 to 1970)

Pt. No.	Age Sex	Underlying Factors	Therapy			Candida Species	Premortem			Postmortem			Outcome
			Dia- betes	Ste- roids	Cy- totoxic Agents	Anti- biotics	Irra- diation	Sus- pected	Non-Diag- nostic Isolation§	Diagnostic Isolation	Positive Cultures	Organ Involvement Histologically	
1	41 M	mult. abd. op.	-	-	-	+	-	-	yes	none	blood, lung	myocardial abscess	DO
2	63 M	mult. abd. op.	-	+	-	+	-	-	yes	blood x7†	lung, brain, kidney, subphrenic abs.	spleen, kidney, peripancreatic abs.	DF
3	49 M	mult. abd. op.	-	?	-	+	-	-	yes	blood x5 peritoneal fluid x1	lung	esophagus, lungs, spleen, kidneys, brain, heart (papillary muscles)	DF
4	55 F	mult. abd. & cardiac op.	-	+	-	+	-	-	yes	CSF pleural fluid	none	pericardial abscess	DO*
5	40 F	mult. abd. & mult. chest op.	-	+	-	+	-	-	no	none	lung, subdiaphragm, phragmatic, & pouch of Douglas abs.	lung, subdiaphragm, pancreat & pouch of Douglas abscesses	DO
6	65 F	mult. abd. op. & carcinoma	-	+	-	+	+	-	yes	none	lung	kidney, colon, brain	DF*
7	67 F	mult. abd. op. & carcinoma	-	-	-	+	-	-	yes	none	none	lung	DO*
8	57 F	mult. abd. op. & carcinoma	-	-	-	+	-	-	yes	blood x2†	abd. wall abscess	lung abs., mitral valve vegetations, brain	DO
9	73 M	mult. abd. op. & carcinoma	-	-	-	+	-	-	no	none	bronchial exudate	myocardium, brain	DO*
10	22 F days	mult. abd. op. & prematurity	-	-	-	+	-	-	no	peritoneal fluid x1	peritoneal cavity	liver surface, jejuno-peritoneal fistula	DF/DO
11	42 M	abd. & card. op.	-	+	-	+	-	-	no	none	mitral & aortic Starr-Edwards valve vegetations	mitral & aortic vegetations, left ventric. & superior mesenteric artery mycotic aneurysms, brain	DF
12	71 M	abd. & chest op.	-	-	-	+	-	-	yes	blood x7	blood	brain	DO
13	74 M	abd. op. & Hodgkin's	-	+	+	+	-	-	yes	none	none	lungs, pleura, liver capsule	DO
14	25 F	abd. op. & SLE	-	+	-	+	-	-	yes	blood x3 peritoneal fluid, hepatic node†	lung, spleen, liver, kidneys, meninges, brain, thyroid, shoulder	cerebellar abscess; systemic histology unavailable	DF
15	47 M	cardiac op.	-	-	-	+	-	-	yes	homograft valve blood x4	none		lived (3 mo. follow)
16	51 M	cardiac op.	-	-	-	+	-	-	yes	homograft valve blood x6	none		lived
17	61 M	chest op.	-	-	-	+	-	-	yes	empyema†	none		lived
18	50 M	heart transplant	+	+	+	+	-	-	yes	none	none	heart, pericard, lungs, pleura, esophagus, thyroid, bladder, pancreas,	DF/DO*

(ALG also)

22	22 F	oper., other	+	-	-	+	-	albicans	+	(150 mg)	yes	yes	retroperitoneal soft tissue passed in nephrostomy†	lung, bladder	spleen, kidney, esoph. lung, pleura lung, kidney	lived
23	7 F	acute leukemia	-	+	+	+	-	albicans	-	-	no	yes	none	lung, bladder	spleen, kidney, esoph.	DF/DO*
24	9 M	acute leukemia	-	+	+	+	-	albicans	-	-	no	no	none	lung	lung, pleura	DO
25	48 M	acute leukemia	-	-	+	+	-	albicans	-	-	yes	yes	aspergillus from marrow	lung	lung, kidney	DO*
26	12 M	acute leukemia	-	+	+	+	-	albicans	-	-	no	yes	none	liver abscess	splenic & parasplenic abscesses	DO*
27	47 F	lymphoma	-	+	+	+	-	albicans	-	-	no	yes	none	lungs	lungs	DO*
28	28 F	lymphoma	-	+	+	+	-	albicans	-	-	no	yes	none	lung	serosa of small bowel, ulcer of lesser curvature penetrating liver	DO
29	56 F	lymphoma	-	+	+	+	-	albicans	-	-	no	no	none	none	spleen, kidneys, liver, stomach, bladder, marrow, lymph nodes; aspergillus in lungs	DF
30	30 M	carcinoma	-	-	-	+	-	albicans	-	-	yes	no	neck abscess	none	lung abscess	lived
31	72 M	carcinoma	-	-	-	-	-	?	-	-	no	yes	none	none	none	DO
32	35 F	SLE	-	+	-	-	-	albicans	-	-	yes	yes	empyema† pleural abscess	none	none	DO
33	23 F	SLE	-	+	+	+	-	albicans	-	+	yes	yes	none	lung, liver, neck	thyroid, spleen, heart; aspergillus in thyroid, lung, brain	DF
34	40 F	Laennec's cirrhosis	-	+	-	+	-	albicans	-	-	yes	no	none	lung, blood	lung, bladder, gastric ulcer	DO
35	66 M	aortic stenosis	-	-	-	-	-	not albicans	-	-	no	no	none	lung	lung, parathyroid connective tissue	DO
36	49 M	nephrotic syndrome	-	-	-	+	-	albicans	-	+	yes	?	meningeal lesion†			lived
37	55 M	pneumonia	-	-	-	+	-	albicans	-	-	yes	?	blood x4	kidney, lung	heart, kidneys	DF
38	13 F days	meningitis	-	-	-	+	-	albicans	-	-	no	no	none	lung	lung	DO*
39	56 M	pemphigus	-	+	-	+	-	albicans	-	-	no	yes	none	lung	lung	DO*
40	38 F days	prematurity	-	-	-	+	-	albicans	-	-	no	no	none	kidneys	lung, kidneys, brain	DF

g—non-diagnostic isolations were obtained from throat and oral cavity swabs, sputum, bronchial secretions, urine and surgical wounds

DF—died of fungus infection

DO—died of other causes

DF/DO—fungus infection was at least a significant contributing factor to the cause of death

*—bacterial septicemia was present just prior to death

†—those blood cultures positive for candida organisms and associated with positive cultures from intravenous catheter tips

‡—those cases in which pre-mortem identification of candida organisms was made histologically in biopsy specimens or closed body fluids

§ FC—5 Fluorocytosine

TABLE 2.—Outcome of Infection as Related to Diagnosis

Premortem	Survived	Died of Fungus	Died of Other Causes	Fungus Contributing Cause of Death	Total
Diagnosed	7	4	4	0	15
Undiagnosed	0	5	16	4	25
Total	7	9	20	4	40

TABLE 3.—Outcome of Infection as Related to Therapy

	Survived	Died of Fungus	Died of Other Causes	Fungus Contributing Cause of Death	Total
Antifungal chemotherapy	5	4	2	0	11
No antifungal chemotherapy	2*	5	18	4	29
Total	7	9	20	4	40

*One improved following drainage of candida empyema; one improved following drainage of candida neck abscess.

during the same period in hospital as that in which the *Candida* infection developed.

In 19 of the cases (47.5 percent), the diagnosis was suspected premortem; in 15 (37.5 percent) of these the diagnosis was established, and in 11 of these 15 specific antifungal therapy was begun. (It can be seen that 33 of the 40 patients (82.5 percent) died and that in 13 (39.4 percent) of the 33 who died, *Candida* infection was considered to be either the primary cause of death or a major contributing factor.) Table 2 illustrates the outcome in the diagnosed and undiagnosed cases, and Table 3 the outcome in treated and untreated cases.

Of significance is the fact that the condition was diagnosed in all seven survivors and they were treated either by specific chemotherapy (five cases) or drainage of abscess and empyema cavities (two cases).

Table 4 presents data on the 11 cases in which specific antifungal therapy was given. In general, diagnosis was made and treatment begun relatively early on the patients who survived, while those who died during therapy were mori-

TABLE 4.—Total Amphotericin Dosage (mg/kg)

Pt. No.	Survived	Died of Fungus	Died of Other Causes
2		0.28	
3		5.3	
4			0.29 gm/kg*
14		0.76	
15	7.9		
16	29		
19			4.8
20	5.8		
22	2.7		
33		1.3	
36	33		
mean dose	15.68	1.91	

*5 Fluorocytosine

TABLE 5.—Principal Underlying Factors in Patients with Systemic Candidiasis

Disease or Condition	No. Cases
Surgery, abdominal	14
Surgery, other	10
Organ transplant	2
Lymphoma	4
Leukemia	4
Carcinoma	6
SLE	3
Prematurity	2
Miscellaneous	7

bund at the time of diagnosis and initiation of therapy.

Table 5 lists the underlying factors present in the 40 patients. Surgical operation was a factor in 50 percent of the total. Table 6 summarizes the sites from which diagnostic isolates were obtained premortem in the 15 diagnosed cases and Table 7 the organ involvement at postmortem examination in the 32 patients in which *Candida* was present. The lung was the organ most frequently involved as in our previous experience² but contrary to the reports of Louria et al,⁹ in which the kidney was described as most frequently infected. In ten of the cases a single organ was involved, while in 21 cases two or more organs were affected. In case 14 (Table 1) only brain histology was available, and in case 32 *Candida* organisms were isolated premortem from an empyema cavity but were not demonstrated at postmortem.

TABLE 6.—Methods of Diagnostic Demonstration of Candida Organisms Premortem

Blood culture	8
Tissue histology	4
Abscess culture	3
Empyema histology	2
Peritoneal fluid culture	2
Homograft valve culture	2
CSF culture	1
Pleural fluid culture	1

TABLE 7.—Organ Involvement at Postmortem

Organ	No. Cases
Lung	16
Kidney	9
Brain	9
Heart	9
Myocardium	7
Endocardium	2
GI tract	8
Spleen	6
Peritoneal cavity	6
Liver	3
Pleura	3
Bladder	3
Thyroid	2
Pancreas	2
Pericardium	2
Bone marrow	1
Prostate	1
Lymph nodes	1
Blood vessel	1
Single organ	10
Multiple organ	21

Thirty-eight of the 40 patients were compromised by at least one therapeutic modality, and the other two (Cases 31 and 35) had significant underlying diseases—carcinoma and aortic stenosis, respectively. Surprisingly, only two of the patients were diabetic. Three of the patients had a concomitant Aspergillus infection.

Prevalence of Candida in saliva specimens

The data obtained from the saliva cultures are shown in Tables 8 and 9. Because of the relatively small numbers involved, the only statistically significant difference in carrier frequency was found between the control group and the multiple therapeutic modality group (29 percent versus 55 percent, $p < .025$). While only 29 percent of the control group grew Candida spe-

TABLE 8.—Candida Isolates from Saliva: Comparison of Frequencies of Occurrence in Patients Grouped by Therapeutic Modality

	Total	CA†	CNA‡	Total with Candida Species	Percent Positive
Controls	30	9	0	9	30
Miscellaneous illnesses, untreated	21	6	1	6	29
Antibiotics	14	5	0	5	36
Steroids	10	6	2	6	60
Cytotoxic agents	14	5	1	6	43
Radiation	18	4	2	6	33
Antibiotics and steroids ...	9	4	0	4	44
Antibiotics and cytotoxic agents	6	4	1	5	83
Steroids and cytotoxic agents	12	5	1	6	50
Antibiotics, steroids and cytotoxic agents	6	2	1	3	50
Radiation and antibiotics ..	2	2	0	2	100
Radiation and steroids ...	3	2	0	2	67
Radiation and cytotoxic agents	2	1	0	1	50
Radiation, steroids and cytotoxic agents	2	0	0	0	0
	149	55	9	61	

†Candida albicans
‡Candida species, not albicans

cies from their saliva, 41 percent of the single therapeutic modality group did. This difference was not, however, statistically significant (Table 8). When the patients were grouped by disease entities, 43 percent of the lymphoma/leukemia group, 41 percent of the carcinoma group, 42 percent of the rheumatic disease group, and 48 percent of the miscellaneous group were salivary carriers of Candida species, but these prevalences were not statistically different from the control group (Table 9).

Discussion

The difficulty in establishing the diagnosis of Candida infection before death has been frequently emphasized, and the importance of making the diagnosis is underscored in this study by two pieces of data: (1) the seven survivors were all diagnosed and treated before they became terminally ill, and (2) systemic candidiasis appeared to be either the primary cause of death or a major contributing factor in 13 of the 33 patients (39.4 percent) who died. The patient population in which these systemic infections occur has been well defined, and yet in only approxi-

TABLE 9.—*Candida* Isolates from Saliva: Comparison of Frequencies of Occurrence in Patients Grouped by Disease Entity

	Total	CA†	CNA‡	Total with <i>Candida</i> Species Positive	Percent Positive
Normal controls	30	9	0	9	30
Lymphoma	40	15	4	18	45
Leukemia	7	2	0	2	27
Carcinoma	22	7	2	9	41
Connective tissue disease ..	19	8	2	8	42
Diabetes	3	1	0	1	33
Non-fungal infection	6	3	0	3	50
Renal disease	2	0	0	0	0
Miscellaneous	20	10	1	11	55
Total	149	55	9	61	

†*Candida albicans*
‡*Candida* species, not *albicans*

mately half of the patients in this study was candidiasis suspected before death.

Histological, bacteriological and immunological techniques have been evaluated in an effort to facilitate the diagnosis of *Candida* infections. Diagnosis of disease due to *Candida albicans* can be made by the demonstration of both yeast and mycelial elements in tissue sections.^{17,18,19} Taschdjian et al maintain that the demonstration of mycelial and yeast elements, when present together in smears obtained from the oral and vaginal mucous membranes, feces in the presence of diarrhea, body fluids (cerebrospinal, pleural, peritoneal, and ascitic fluid), and skin lesions, is pathognomonic for *Candida albicans* infection, in contrast to colonization.²⁰ They emphasize, however, that such a combination obtained from sputum, bronchial secretions, and catheter or midstream urine is not pathognomonic.²⁰

Bacteriological methods have also been applied to the study of clinical specimens in an effort to identify *Candida* infection. In fact, *Candida* is the fungus most frequently isolated from clinical material, and a major diagnostic problem is the interpretation of reports of positive cultures. The frequency of occurrence of *Candida albicans* in different anatomic locations was summarized by Taschdjian et al.²⁰ The organism can be isolated from 20 percent to 50 percent of normal oral cavities and gastrointestinal tracts.²⁰ It should be emphasized that *C. albicans* is only rarely (0.4 to 4 percent of cases) isolated from normal skin in persons less than 60 years of age.²⁰ This fact should be borne in mind when interpreting blood cultures positive for *Candida* organisms.

The problem of interpretation of culture reports is further compounded by the therapeutic modalities to which patients at risk for *Candida* infection are subjected. Many workers have demonstrated an increase in the number of patients from which *Candida* can be isolated from oral cavity, saliva, and sputum cultures following antibiotic therapy.²¹⁻²⁴ We were unable to locate definitive data on the effect of steroids, cytotoxic drugs, or head or neck irradiation on the incidence of *Candida* organisms in oral cavities.

Our data revealed that patients on either antibiotics, glucocorticoids, cytotoxic agents, or head and neck radiation therapy alone are more likely than a control group to have *Candida* organisms in their saliva. These differences, because of the small number of patients, were not statistically significant. However, those being treated by two or more of these therapeutic modalities were significantly more likely to yield *Candida* organisms on culture of their saliva. This may not be a cause and effect relationship, since these patients were those who also had the most severe underlying nonfungal illnesses.

Isolation of *Candida* organisms from the oral cavities of patients at risk for deep *Candida* infections, therefore, is quite likely to occur and, in fact, isolates of *Candida* organisms considered nondiagnostic were obtained in 25 of our 38 patients (66 percent) in whom appropriate cultures were obtained. Taschdjian et al reported that *Candida* organisms were isolated from foci where they may constitute part of the normal flora in 75 to 80 percent of their cases of systemic candidiasis.²⁰ A positive culture for *Candida* organisms from a normally inhabited focus in a compromised host should alert the clinician to the possibility of *Candida* infection but is certainly not diagnostic, whereas cultures of *Candida* organisms from skin lesions, blood, cerebrospinal fluid, pleural, peritoneal, and ascitic fluid, and pus from closed abscesses are pathognomonic of infection with this organism.²⁰

Numerous immunological and serological diagnostic techniques have been evaluated for efficacy in detection of *Candida* infections. Skin tests with various antigenic preparations are generally acknowledged to be of no diagnostic value.^{25,26,27} A positive reaction indicates past exposure to the organism but does not differentiate between the presence of the organism in the oral cavity and a systemic infection, while a negative

reaction may indicate either no significant past association with the organism or overwhelming infection.²⁸ Lewis et al reported that 46 percent of 192 patients free of fungus infections had a delayed skin reaction to oidiomycin and that only 57 percent of 42 patients with a superficial infection due to *Candida* had a positive reaction,²⁹ while Good et al reported a 57 percent incidence of delayed reactivity to *Candida albicans* antigen in 208 patients in hospital.³⁰ Shannon et al found that 31 (94 percent) of 33 healthy adults manifested delayed hypersensitivity reactivity to a commercially prepared *Candida albicans* antigen and suggested that this skin test antigen might be useful in measuring the ability of an individual to manifest delayed hypersensitivity.³¹

Several serological methods have been analyzed for diagnostic potential with respect to *Candida* infections. Both a complement fixation³²⁻³⁴ and indirect fluorescent antibody^{35,36} technique have been described but are limited in that neither attains ideal separation of carriers from infected patients or patients with cutaneous infections from those with systemic involvement.

The two serological techniques which seem to hold the most promise for the early diagnosis of systemic *Candida* infections are the determination of agglutinin and precipitin titers. Conflicting reports on the value of agglutinin titers exist. Salvin²⁸ stated that *Candida* agglutinins cross-react with antigens from other fungi, and both he and Louria²⁷ concluded that agglutinin titers were of no diagnostic value. Todd found that sera of 22.5 percent of 1150 healthy persons agglutinated *Candida albicans*, that a high titer was correlated with the presence of the organism in the mouth or throat, and that more females than males possessed these agglutinins.³⁷ Other investigators have obtained similar results in normal people.^{38,39} Comaish et al reported that of 18 patients with titers of $\geq 1:16$, all had *Candida* species isolated from cutaneous sites and 16 of these were clinically suspected of having superficial *Candida* infections; their report contained no cases with systemic infections.²⁵ In addition to being positive in some normal persons, agglutinin titers have been demonstrated in cases of pulmonary tuberculosis and histoplasmosis, and in experimental *Torulopsis glabrata* infections.^{20,40}

In contrast to the studies mentioned above, a definite value for the agglutination method is suggested by the work of Preisler et al, who dem-

onstrated at least a two-tube (four-fold) rise in agglutinin titer in 14 of 23 cases of acute leukemia with concomitant systemic *Candida* infection.¹⁵ A two-tube rise in titer was not demonstrated in any of their ten patients without *Candida* infection. These promising results suggest that this technique deserves further evaluation.

The demonstration of precipitating antibody to *Candida* organisms in human sera was long thought to be of no diagnostic value.^{26,27} However, Stallybrass, employing soluble antigen (antigen C) from *Candida albicans*, was able to demonstrate precipitins in the serum of the only patient in his series with systemic candidiasis by a double diffusion technique.⁴¹ None of the other 833 patients, including 15 with mucocutaneous candidiasis, had demonstrable precipitins. Taschdjian et al prepared an antigen (S antigen) consisting of soluble cell wall and cytoplasmic components from *Candida albicans* and demonstrated precipitins in five of eight patients with proved or presumptive candidiasis.^{42,43} The three patients who did not have precipitins had an acute onset and rapid course of infection, and one of these had no demonstrable *Candida* organisms at post-mortem examination. Of ten patients without systemic candidiasis, nine had no demonstrable precipitin antibodies to S antigen by the double diffusion in agar technique. The tenth patient had a *Candida* granuloma. In their total series of 50 cases of systemic candidiasis,²⁰ 88 percent had demonstrable precipitin titers. Agglutinin titers were $>1:160$ in 80 percent of the 47 patients in whom they were determined. (It is noteworthy that only 50 percent of these patients had positive blood cultures pre-mortem.) In their control subjects (51 with superficial candidiasis, 22 with advanced pulmonary tuberculosis, three with actinomycosis, three with cryptococcosis, four with autoimmune hypoparathyroidism and hypoadrenalism, and 17 normals) only eight had precipitins directed against S antigen.⁴⁴ One of these was the previously mentioned patient with *Candida* granuloma, while the other seven were children with chronic cutaneous and mucocutaneous candidiasis. In another study, Murray and Buckley tested the sera of 40 subjects for *Candida* precipitins and demonstrated them only in their two cases of systemic candidiasis.⁴⁶ They were unable to demonstrate precipitins in 160 sera which they obtained from a blood bank. The nature of their antigen was unspecified.

More recently these same workers, using the double infusion technique, studied precipitins in the sera of 68 patients who had had open-heart operations.⁵¹ None of the 47 patients tested preoperatively had precipitins, and all of 6 who had *Candida* endocarditis were among the 33 who developed these precipitins. The investigators concluded that demonstration of these precipitins in patients following operations on the heart should alert clinicians to the possibility of *Candida* endocarditis and suggested that the false positive tests may be due to insertion of an infected valve, proliferation of *Candida* organisms on mucosal surfaces following antibiotic therapy, or a transient postoperative candidemia.

Precipitin titers are low, usually within the range of 1:1 to 1:4, rarely exceed 1:8, and disappear with recovery from the infection.⁴⁵ The level of the precipitin titer is not proportional to the severity of infection and cross reactions are limited to other members of the *Candida* species.¹⁶ Precipitins have not been found in patients with superficial candidiasis in the absence of autoimmune endocrinopathies.²⁰

Although the studies mentioned above suggest that the precipitin test might be a useful method for diagnosis of systemic *Candida* infection, several other studies question its validity. Chew and Theus, using the more sensitive Prier tube method and purified mannan antigen,* were able to demonstrate precipitins in 15 of 31 sera from healthy adults, in 43 of 62 patients with mucocutaneous candidiasis, and in 10 of 10 sera from healthy adults that had been concentrated 15-fold.⁴⁷ The Ouchterlony plate technique, on the other hand, revealed precipitins in only one of 31 unconcentrated sera from uninfected subjects, six of 62 from patients with mucocutaneous candidiasis and three of ten concentrated sera. These workers also demonstrated precipitins against S antigen in concentrated pooled human γ -globulin and concluded that all healthy adults have precipitins directed against *C. albicans* mannan demonstrable in their serums if sensitive detection techniques are employed. Pepys et al, also using *C. albicans* mannan as an antigen and the double diffusion technique, demonstrated precipitins in sera in 25 percent of asthmatics, in 33 percent of asthmatics with pulmonary eosinophilia, in six percent of patients with miscellaneous lung diseases,

and in 4.5 percent of 22 healthy controls.⁵⁰ Their antigen is different from S antigen, but they point out that S antigen does contain some mannan. They concluded that technical factors—for example, the use of a highly concentrated antigen preparation—may have prevented Stallybrass and Taschdjian et al from detecting low concentrations of precipitins present in sera from some of their normal controls.

Another challenge to the reliability of the precipitin reaction comes from Preisler et al, who were able to demonstrate precipitins in only four of their series of 23 acute leukemics with systemic candidiasis, while they demonstrated a significant rise in agglutinin titers in 14 of these patients.¹⁵ Taschdjian et al report that some of their precipitin containing sera that were kept frozen for more than six months showed a partial to total loss of precipitating activity and suggest that this same process may have occurred in Preisler's retrospective study.²⁰ Nonetheless, precipitins were present in the sera of only six of Taschdjian's nine acute leukemics with systemic candidiasis.

The serious problem of our inability to diagnose systemic *Candida* infection even in the presence, in a given patient, of positive cultures from sputum, urine, and blood when intravenous catheters are present, and the fact that many of our own patients whose *Candida* infection was undiagnosed premortem, even though multiple organs were involved, emphasizes the necessity for the development or refinement of specific diagnostic techniques for the demonstration of this disease in man. It is obvious that a prospective study of the reliability of the detection of *Candida* precipitins and agglutinins in the diagnosis of disseminated candidiasis is necessary. In the interim, the precipitin test employing the S antigen and double diffusion as employed by Taschdjian et al would seem to be the most reliable diagnostic tool presently available for the detection of systemic *Candida* infection, especially if potential occasional false negative results and false positive results (in asthmatics, postoperative heart patients, and patients with *Candida* granulomas or autoimmune endocrinopathies with superficial *Candida* infections) are recognized. This test may be of value in those cases in which several positive blood cultures for *Candida* organisms are obtained, as a positive test would assist the physician in deciding whether the pa-

*Mannan is a highly branched polymer of mamose and is a major surface antigen of *Candida* organisms.^{45,49}

tient merely has transient candidemia⁵² or has a disseminated infection. In our laboratory, Dr. J. David Gaines has been evaluating the precipitin method for one year. Approximately a hundred patients have been tested thus far, and 13 had positive result. Of these 13, ten were found to have documented systemic candidiasis. As yet we have not evaluated the data for potential false negative results.

Finally, the importance of an early diagnosis and treatment of systemic *Candida* infection is apparent, since none of the patients in the present study and few patients in other studies survived their systemic *Candida* infections without the benefit of specific antifungal therapy.

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Deaths During Skin and Scuba Diving In California in 1970

JAMES M. LANSCHÉ, M.D., *Oakland*

■ *An investigation of 30 recorded deaths in sport diving in California in 1970 gave evidence of equipment failure in two, a failure of the victims' judgment or training in 13, and a failure of rescue attempts in four instances. In three histories no cause could be found. Factors associated with the deaths are reported. In the same period there were recorded in the state 171 drownings in home pools out of a total of 712 drownings in water sports.*

THIS REPORT IS TO ASSESS the magnitude of the health problem of sport diving in California and to investigate the causes of failure of the mechanisms designed to provide survival for those entering the alien environment beneath the sea.

The degree of danger of sport diving compared with automobile driving was estimated by Schenck, McAniff and Carapezza.¹ On a basis of man-hours involved in each activity, they concluded that diving was 96 times more dangerous than driving an automobile.

The underwater world is receiving ever increasing popular interest because of the emphasis on the adventure and beauty to be found in the sea. Equipment and instruction is now readily available to permit entrance to this world for many people. California, with its population centers, suitable weather and waters, invites participation in this sport for large numbers. The hazards of the sport and the techniques of coping with these problems are outlined in diving courses for the participant. There are several excellent reviews available for physicians who

need to be aware of the special problems in the treatment of diving accidents.^{2,3,4,5,6} The public health aspects of diving are reported in reviews for California and the United States as a whole.^{1,7,8}

Method

The Bureau of Sanitary Engineering of the Department of Public Health of the State of California makes an annual survey of drownings in the state.⁹ This information is necessarily limited to the data on the Certificates of Death collected by the department. From this information it was possible to obtain autopsy protocols and summaries of the circumstances leading to the victim's death from the coroners of the counties in which the deaths occurred. Information was provided by Mr. C. C. Hill of the County of Monterey on one death and by Doctor Thomas T. Noguchi of the County of Los Angeles on seven deaths which were not included in the Bureau of Sanitary Engineering's report. One victim included in the Bureau's report was removed from this study because he was only six years old and even though the accident involved

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Reprint requests to: J. M. Lansche, M.D., 411-30th Street, Suite 306, Oakland, Ca. 94609.

TABLE 1.—Incidence of Drowning in Water Sports in California

Year	Population in Millions	Total	Diving
1962	16.9	430	15
1963	17.5	489	21
1964	18.0	503	12
1965	18.5	495	24
1966	18.9	473	18
1967	19.3	659	15
1968	19.6	656	15
1969	19.9	717	17
1970	20.0	712	23

the use of a weight belt, he could not be considered to be diving. A total of 30 instances of death during skin and scuba diving were accepted as the basis for this report. Though not always specific, the protocols suggested 25 victims were scuba diving and three were probably breathe hold diving. In two, it was not clear. All deaths recorded are used without further classification in the comparisons which follow. For various reasons, little or no information could be obtained about some victims. These are listed as unreported data. An attempt is made to classify the primary factors causing the accidents into groups based on failure of equipment, failure of judgment of the victim, failure of training of the victim, or failure in rescue. In some instances details that would bear on this classification were not available and these victims were omitted from that portion of the report.

Results

Over the eight years between 1962 and 1970 the population of the state and the number of drownings in water and sports diving¹⁰ increased (Table 1).

From the Bureau of Sanitary Engineering's report it is possible to identify the recreational activity in which the victim drowned (Table 2) as well as the location of the accident (Table 3).

Thus, of a total of at least 712 fatal accidents occurring in water sports, 30 were associated with skin and scuba diving. One hundred seventy one deaths occurred in home pools and 39 in public pools. Of course, what cannot be retrieved from these figures is the incidence of drowning in the population using home and public pools, and the incidence of fatal accidents in the sport diving population.

TABLE 2.—Activity in All Deaths by Drowning, 1970

	Number
Swimming and Wading	236
Boating	92
Diving	22
Total	350
Unknown	362
Total	712

TABLE 3.—Locations in All Deaths by Drowning in 1970

	Number
Home pools	171
Public pools	39
Ocean	109
Lakes	138
Rivers	143
Other	212

TABLE 4.—Causes of Death in Diving

Cause of Death	Number
Drowning	23
Air Embolism	5
Bends	1
Hemopneumothorax	1

The incidence by county reflects the population of the area and suitability of nearby water. The incidence of deaths by month of the year showed a random scattering with a tendency toward an increased number in the late months of the year.

The causes of death are reported in Table 4. The principal cause of death was drowning, occurring in 23 victims. The autopsy protocols were definite about air embolism in five and a hemopneumothorax in one, and the history and autopsy findings suggested the bends in one. There was one example of asphyxia without water inhalation or pulmonary edema. Acute ethanol intoxication was found in one victim and a trace of alcohol in the blood of another.

There was one history of hypertension reported. No evidence of myocardial infarction or primary cerebral disease was found in the autopsies. There was one report of cirrhosis of the liver. The heart showed moderate hypertrophy (a weight at least 25 percent greater than maximum normal) in two when compared with standard tables of maximum heart weight.¹¹ Two

TABLE 5.—Incidence of Sport Diving Deaths by Age and Sex

Age	Male	Female	Total
10-15	1		1
16-20	4		4
21-25	3		3
26-30	4	1	5
31-35	4		4
36-40			0
41-45	9	1	10
46-50	1		1
51-55			0
56-60	1		1
Unknown			1

TABLE 6.—Time and Depth of Recovery of Victims of Sport Diving Drownings

Depth of Recovery	Immediate	Less than one hour	Over one hour	Unknown
Surface	6	3	0	0
Less than 30 feet	2	3	2	1
Deeper than 30 feet ..	0	1	2	1
Unknown	0	0	4	5

hearts were slightly above maximum limits. All victims with enlarged hearts were 41 or older. In the one victim with a history of hypertension, the heart was not above the maximum.

In the comparison by age and sex (Table 5) it was found that the deaths were predominately in males, with a scattering at random in the early years. The youngest age was ten. There was a suggestion of a peak of incidence at age 41 to 45. In the group of 41 and older, the summaries suggested excessive fatigue was a factor in two.

Of interest because of the potential for prevention of the accidents is the time interval from the onset of difficulty or disappearance to recovery of the victim and the depth at which the victim was recovered (Table 6). Of those found on the surface, two were victims of air embolism, and in the others the autopsy evidence was of drowning only. Attempts at immediate search and rescue were provided by companions in 16 cases, were unreported in ten, and by life guards or rescue teams, and by the Coast Guard in the remainder. Transport of the victims was usually by Coast Guard equipment or by boat.

The experience of the diver related to the incidence of death is described in Table 7.

TABLE 7.—Incidence of Sport Diving Drowning Related to Degree of Experience

Experience	Number
Student	3
Novice	3
Less than one year	1
Greater than one year	4
Professional	2
Instructing	2
Unreported	15

TABLE 8.—Systems Failure Groupings in Sports Diving Drownings

System	Number
Failure of Equipment	2
Failure of Judgment	5
Failure of Training	8
Failure of Rescue	4
Undetermined	3
Evidence unreported	8

Among the students, one became entangled in kelp while practicing alone after class. Another took his regulator from his mouth for unknown reasons and immediate rescue and revival attempts were unsuccessful. The third was in class on the surface, in no apparent distress, but stopped swimming and could not be revived. There was no post mortem evidence of air embolus and the cause of death was given as drowning in all three.

To investigate the prime cause of the accident and major related factors was difficult. An attempt was made to assign the victims into systems failure groups according to failure of equipment, failure of judgment, failure of training, and failure of rescue (Table 8). In 19 reports there was a basis for assignment. In eight reports, not enough evidence was submitted to permit classification. In three more, no deduction could be made though there was information available from witnesses and from post mortem examinations.

In one of the two cases of failure of equipment, a broken face mask with a surface-supplied air source appeared to be the cause. In the other a life vest failed to inflate, making rescue more difficult, but the victim's original problem could not be determined. The errors in

judgment that were conclusive were swimming or diving alone. One victim became entangled in kelp and another in his fishing line while diving alone. Another drowned while breath-hold diving alone, but his blood alcohol level indicated intoxication. One did not return from snorkeling alone and another was found dead on the surface after diving alone.

In the training failure group a decision is difficult between a failure of training to prepare a diver and a failure of the diver to judge properly on the basis of his training. Two victims of separate accidents died during their third dive of the day. One was found drowned on the surface and the other, who died of an air embolus, was said to have panicked at a depth of 100 feet. The depth and duration of the dives was not otherwise reported. Two other victims of air embolus were included in the training failure group, but in only one was the ascent recorded as "too fast." Another accident difficult to classify but included in this group was that of a diver assisting in an underwater class who left the group and was observed to be having difficulty but sank before help could be offered. More obvious failures of training was a case in which the diver sank from the surface when unable to free himself from his equipment. Another diver failed in ability to buddy-breathe when out of air and struggled out of a rescuer's grasp on attempt at ascent. The last victim in this group became tired in the water following an instructional dive. His companion brought aid to him, but he was found drowned on the surface. A failure of physical conditioning, judgment, training or rescue could be involved.

Rescue failures included a second victim entangled in kelp, but availability of immediate aid was unreported. A novice in a training class took his regulator from his mouth for unknown reasons and drowned. Immediate rescue attempts were unsuccessful. In one case the diver was unable to escape from an underwater vehicle, and in another it was impossible to hold an injured diver in surf.

In three instances the cause of death is puzzling: The victims were on the surface, swimming and in no apparent distress. One disappeared from his two companions. Rough water and fatigue may have played a part. A victim in his early forties, returning early from a class, was observed to suddenly stop swimming and was

found drowned on the surface. Fatigue may have played a part. Another, having completed a dive assisting an instructor in a class, disappeared from the surface. No evidence of previous distress, physical ailment, fatigue or decompression sickness could be found.

Conclusions

There is difficulty in obtaining knowledge of the prime cause and the various events that lead to a victim's death. A study investigating only deaths by drowning will possibly omit instances of air embolism and bends. The implications for proper physical conditioning and thorough training before entering the sea is apparent in this report. Increased endurance, the use of the buddy system, experience in the use of equipment, signals of distress, and buddy-breathing, together with knowledge of decompression sickness might have helped avoid 17 of the accidents in which data could be obtained.

Even with experienced witnesses and trained investigators, the causes and contributing factors may not be apparent. Information by the investigating officers should include depth and duration of the dive in which the accident occurred, as well as in the preceding dives in a 12-hour period if the problem of decompression sickness is to be investigated. The autopsy surgeon may need to open the great vessels under water to note the tell-tale bubbles of air embolism and bends. The equipment and air supply left in the tanks should be inspected for failures, exhaustion of air or purity of air source if the causes of deaths due to equipment failure or inhaled intoxicants are to be discovered. An excellent form covering these and other factors necessary to understand the cause of death in divers has been developed.¹

Instructors must be responsible for eliminating from the sport novices who are physically unable to perform because of lack of endurance or immaturity. Sea training should not be permitted without demonstration of swimming ability and endurance. Certification should not be given without a demonstrated knowledge of decompression sickness and of the use of the Decompression Tables, as well as ability in rescue and resuscitation.

The public health and safety implications are apparent. It is the responsibility of articles in diving publications to alert the reader to safety

problems, of diving clubs to advise members of the hazards they must endure, of physicians engaged in diving to instruct their community in the health problems of the sport, and of the producers of the excellent motion pictures and television programs to provide reminders of the pitfalls that await the careless and ignorant.

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ARTERIAL HYPOXEMIA

What is the critical level of arterial hypoxemia?

I had heard some physicians label a PO_2 below 50 as respiratory failure. Yet those of us who treat a lot of pulmonary diseases will see patients walk in, sometimes to an outpatient clinic, and find their PO_2 is 46. They are getting along; I'm not saying they are roses; but they are getting along.

What I was able to find is that in the otherwise normal individual who is able to respond with cerebrovasal dilatation, one of the compensatory mechanisms for hypoxia, the lowest tolerable arterial PO_2 is probably around 27 mm of mercury. This fits apparently with the experience of men on Mt. Everest who were able at least for a short period to remain conscious without supplemental oxygen.

In patients with severe respiratory disease . . . who may have already developed another compensatory mechanism, namely polycythemia, and already have maximal cerebrovasal dilatation, it is said that the lower limit of arterial PO_2 would be about 20 mm; that is getting down mighty low.

—ATTILIO D. RENZETTI, JR., M.D., Salt Lake City
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Medical Progress

Disaccharidase Deficiency in Health and Disease

RAYMOND HERBER, M.D., *Loma Linda*

DISACCHARIDE INTOLERANCE with subsequent "fermentative diarrhea" was reported in the early literature, but was considered to be primarily of a temporary nature and limited to the pediatric group.¹ More than 50 years ago Starling² observed that the hydrolytic activity of the intestinal juice is inadequate to account for the rate of disappearance of disaccharides from the lumen. In 1935 Cajori³ demonstrated this process more clearly in dog studies, but it remained for Borkström and Dahlqvist⁴ in 1957 to clearly localize the hydrolysis to the intracellular portion of the intestinal tract. Following this observation, the first clinical application was made in 1958 with the report of intestinal lactase deficiency in humans.⁵

Since then the scope of this problem has been enlarging rapidly each year. New ramifications vary from foreign aid grants of dairy products to under-developed countries⁶ with high lactase-deficiency rates to the treatment of osteoporosis.⁷ It must be remembered that most of man's caloric needs are supplied by carbohydrates. In regions of low living standards, up to 80 percent of the total caloric intake is in carbohydrate form. Even in countries with high standards of living, about 50 percent of the dietary calories are obtained from carbohydrates. The chief dietary carbohydrates are the polysaccharide, starch, and the disaccharides, sucrose and lactose. The more im-

portant food sources of each of these complex carbohydrates has been reviewed by Harding et al.⁸

Specificity of Intestinal Disaccharidases

The existence of several different α -glucosidases has been demonstrated in extracts of intestinal mucosa.⁹⁻¹⁹ These enzymes have varying specificity for disaccharides with α -D-glucopyranoside structure (for example, maltose, sucrose, isomaltose, trehalose), and thus the intestinal hydrolysis of these sugars is caused by a complicated enzyme mixture.

The β -glucosidase and β -galactosidase activities of extracts of intestinal mucosa seem to be exerted by three enzymes, of which only two are lactases,¹⁶⁻²¹ and only one has significant lactase activity at the usual intestinal pH of 5.8.²⁰

Dahlqvist pioneered in the separation of the disaccharidases of the intestinal mucosa. He characterized them first in hog mucosa¹¹ and then in human intestinal mucosa obtained from surgical specimens.¹⁷ He separated the enzymes by selective heat inactivation; other investigators added gel filtration chromatography.^{18,19} Using different methods of separation and characterization, the group in Sweden¹⁷ and the group in Zürich^{18,19} have arrived at slightly different classifications for the enzymes (Table 1).

Gray,^{20,21} using density gradient centrifugation, found three β -galactosidases, all having different molecular size, enzyme I being the largest and enzyme III the smallest. Of the three β -galactosidases in human intestine only I and II are ca-

From the Section of Gastroenterology, the Department of Medicine, Loma Linda University School of Medicine.

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Reprint requests to: R. Herber, M.D., Department of Medicine, Loma Linda University, Loma Linda, Ca. 92354.

TABLE 1.—*Specificity of the Human Intestinal Disaccharidases*¹⁷⁻¹⁹

Enzyme and Substrates		Percentage of Total Activity Against Each Substrate
Nomenclature of Semenza and Auricchio ^{18,19}	Nomenclature of Dahlqvist ¹⁷	
Maltase 1	Maltase III Maltose	10
Maltase 2	Maltase II Maltose	15
Maltase 3 = Sucrase 1	Maltase I b = Sucrase Maltose Sucrose	25 100
Maltase 4 = Sucrase 2		
Maltase 5 = Isomaltase = Palatinase	Maltase I a = Isomaltase = Palatinase Maltose Isomaltose	50 100
Lactase 1 = Cellobiase 1 = Gentiobiase 1	Lactase = Cellobiase = Gentiobiase Lactose Cellobiose	100 100
Lactase 2 = Cellobiase 2 = Gentiobiase 2		
Trehalase	Trehalase Trehalose	100
Order of appearance on elution from Sephadex G 200 column	Order of increasing heat stability	

pable of splitting lactose, but since enzyme I is peculiar to intestine, has maximum specificity for lactose rather than other β -galactosides and has a pH optimum close to that of intraluminal intestinal fluids, it is quite likely that it is the enzyme responsible for digestion of dietary lactose. The fact that both human liver and kidney contain an enzyme that appears identical with intestinal enzyme II suggests that this is a ubiquitous enzyme perhaps localized in lysosomes. The physiological role of enzyme II is unknown, but human liver β -galactosidase has recently been shown to be deficient in patients with generalized gangliosidosis,²² and liver homogenates from such patients are unable to release galactose from a monosialoganglioside. It is doubtful that it plays any significant role in lactose hydrolysis, since intact disaccharide appears incapable of quantitatively entering the absorptive cell²³⁻²⁵ from either the intestinal or vascular side.

Gray²¹ found that infants have the same constituent β -galactosidases as adults. This is not consistent with the suggestion by Huang and Bayless²⁶ that there is an "infantile" enzyme that

wanes during childhood and an "adult" enzyme that develops later in life. Rather it is probable that man is born with a full complement of intestinal β -galactosidases, two of which are lactases.

Elliott et al²⁷ found two lactase enzymes in ten European children while lactase from nine full-blood aboriginal children consisted of only small amounts of enzyme I. The aboriginal children were lactose intolerant.

Development of Intestinal Disaccharidases

All of the intestinal disaccharidases are already active in the three-month-old human embryo.²⁸ The α -disaccharidase activities reach the normal adult level in the sixth to seventh month of fetal life. The only exception is maltase I, which is still low in the newborn. In most animals studied, the α -disaccharidase activities are still absent or very low at birth.²⁹⁻³² The β -disaccharidase activities reach their maximum in humans toward the end of fetal life. In the adult, the lactase values are occasionally reduced but still sufficient for hydrolysis of a normal lactose in-

take.^{33,35} In animals, the lactase activity develops early in fetal life and drops to very low values (10 percent) in the young animal after weaning.^{32,34}

In human studies³⁶ of populations with a high incidence of lactase deficiency lactase levels decrease following the weaning period and the adult levels are usually reached by 10 years of age. This time interval is extended a few years with higher milk ingestion.

Distribution of Disaccharidases

The finding that disaccharide hydrolysis occurs in the mucosa has naturally led to curiosity about where in the mucosal cells these enzymes are located.

Tissue fractionation has been used by Miller and Crane^{37,38} for the isolation of brush border membranes from the epithelial cells of hamster small intestine. The disaccharidase activities are recovered in high yield in these brush border preparations.

Experiments based on incubation with slices of everted intestine *in vitro* have in most cases been performed with sucrose as the substrate. If a piece of surviving intestine is incubated *in vitro* with a mixture of glucose and fructose, glucose is rapidly absorbed and accumulated in the tissue while fructose is slowly absorbed and does not accumulate. If the intestine is incubated with sucrose, one also finds that glucose is accumulated in the tissue in large amounts while most of the fructose liberated is recovered from the incubation medium.³⁹

In other experiments glucose oxidase has been included in the incubation medium.³⁹ This enzyme does not react with sucrose, but it rapidly oxidizes free glucose to gluconic acid which is not actively absorbed by the intestine. If the invertase were located on the surface of the mucosal cells in direct contact with the incubation medium, the glucose liberated on hydrolysis of sucrose would have become trapped by the glucose oxidase. This did not occur; the accumulation of intracellular glucose during incubation with sucrose plus glucose oxidase was as large as on incubation with sucrose alone.

Another group of investigators found that glucose liberated from maltose is trapped by glucose oxidase under similar conditions.⁴² This may mean that at least one of the maltose splitting enzymes is actually located on the surface of the cell.

Most tissue incubation experiments thus indicate a superficial localization of the disaccharidases, and at least the invertase is not located in direct contact with the medium but rather is located inside some kind of surface membrane.³⁹⁻⁴¹

Ugolev,⁴³ however, has evidence for a sucrase enzyme on the outside of a membrane. This concept is also in keeping with the finding that the molecular diameter of the disaccharides is too large to penetrate the cell membrane, while the enzyme could more rapidly pass out through the cell membrane.

Histochemical staining using synthetic substrates of glycosidase activities was originally described by Seligman et al.⁴⁴ A histochemical staining method utilizing disaccharides as substrates was developed by Dahlqvist.^{45,46} Due to the slow reaction considerable autolysis occurred and made the localization of the stain uncertain, especially in the brush border. Jos et al⁴⁷ in Paris developed a much more sophisticated and superior modification of the disaccharidase activity staining method. With this method, the more intense staining is in the brush border and in the distal part of the villi. Similar observations have been made for other enzymes, such as alkaline phosphatase, non-specific esterase, and leucine aminopeptidase.⁴⁸ It has been argued,⁴⁹ however, that this distribution of the stain for an enzyme activity need not mean that the enzyme is more active in the distal parts of the villi, but may be a reflection of membrane damages in this part of the tissue which cause an increased accessibility of the staining reagents for the enzyme stained.

Studies on isolated brush borders of hamster intestine⁵⁰ with electron microscopy demonstrated 60-angstrom knobs attached to the lumen surface of the plasma membrane. Separation and recovery of the knobs and the plasma membrane are possible. The activities of the disaccharidases invertase and maltase reside in the knobs and are not found with the plasma membrane. These findings have not been confirmed in humans.

Dahlqvist devised a method for assay of intestinal disaccharidases^{51,52} which is easy to use and has close reproducibility in various laboratories.⁵³⁻⁵⁸ There is good correlation between enzyme levels and disaccharide intolerance tests if the biopsy specimen is obtained at the ligament of Treitz or beyond.

Intestinal disaccharidases in human sub-

jects^{33,57,61} with a variety of disorders were assayed in surgical and peroral biopsy specimens from the duodenum, jejunum, and ileum. There was practically no activity in the first portion of the duodenum, but the disaccharidases then gradually increased to maximal activity in the first part of the jejunum and remained constant into the proximal ileum, but decreased in the distal ileum to 50 to 75 percent of the maximal activity. The sucrase to lactase (s/L) ratio^{60,61} was stable along the entire intestine. In the lactase-deficiency subjects the decrease in enzyme persisted along the entire intestine. No disaccharidase activity was found in the stomach or colon, but small amounts of maltase activity⁵⁹ have been noted in kidney, and, to a lesser extent, brain, pancreas, and liver.

It has been observed⁶⁰ that the specific activity of disaccharidases obtained at operations are only about one-half of those obtained with peroral biopsy. The s/L ratio, however, is almost identical between the groups. Since there is such low disaccharidase activity in the proximal duodenum, the ratio of s/L or of maltase to lactase in a single specimen can be helpful in the identification of lactase deficiency. These ratios in the lactase-deficient group do not overlap those in the normal groups.^{57,58,61,75} The s/L ratio was less than 4 to 1 in normal subjects and greater than 4 to 1 in lactase-deficient subjects.

Hydrolysis and Absorption of Disaccharides

In contrast to the rapid hydrolysis and absorption rates for sucrose and maltose in normal subjects,^{62-66,68} lactose hydrolysis occurs at rates that are only about half of those for the other disaccharides so that absorption rates for the glucose and galactose products are appreciably below those found when the equivalent monosaccharide mixture is infused. This suggests that the hydrolysis step is rate-limiting in the overall process of lactose hydrolysis-monosaccharide absorption, whereas hydrolysis is apparently not the rate-limiting step for sucrose or maltose absorption.^{62,63}

These studies are compatible with *in vitro* assays of human intestinal homogenates which show lactase to be only 50 percent of sucrase activity.⁵¹

Considering the relatively slow lactose absorption in normal subjects, the rise in blood sugar

concentration after lactose ingestion cannot be expected to be comparable to that found after ingestion of other sugars. Indeed, these findings may explain the fact that about 20 percent of persons with normal intestinal lactase activity show little increase in blood sugar after ingestion of lactose.⁶⁷

Lactase activity is inhibited^{10,69} by a variety of monosaccharides. Lactase is inhibited by all three major dietary sugars—glucose, galactose, and fructose. However, sucrase and maltase are most inhibited by hydrolytic products of their natural substrate. Inhibition is maximal at pH 6.0, the pH normally found in the upper intestine.^{70,72}

Monosaccharide inhibition of lactase may be of some physiologic importance. This suggestion is supported by the fact that after a standard meal the concentration of glucose in the jejunal lumen is about 20 to 40 mM,⁷¹ a concentration in the same range as the K_1 for glucose.

London et al,²⁴ using ¹⁴C lactose, failed to resolve the question of whether in mammalian intestinal mucosal cells there is a β -galactoside permease as well as a β -galactoside hydrolase. In lactase-deficient and normal subjects there was no evidence that lactose may be taken into the cell against a concentration gradient. A permease lack would explain the temporary sugar intolerance seen in children who still retain normal disaccharides activity.⁹²

Almost 50 percent of patients with osteoporosis have a deficiency of the intestinal enzyme lactase.⁷³ To check on this observed relationship, Condon et al⁷ did calcium studies in lactase-deficient subjects. When lactose was administered orally in quantities sufficient to cause mild diarrhea, fecal calcium and fat increased and calcium balance became negative. However, in American Negroes the incidence of intestinal lactase deficiency is high, but the incidence of osteoporosis is low,⁷³ and in this instance there is no association between lactose intolerance and osteoporosis.

Drug absorption⁷⁴ was decreased slightly when diarrhea was induced either with lactose or with saline cathartics in lactase-deficient subjects. Also, it has been reported that lactose is a frequent filler in pharmaceuticals, so it may cause diarrhea and malabsorption on this basis⁷⁵ in lactase-deficient patients.

Pathophysiology and Symptomatology

If one or more disaccharidase enzymes are deficient, the corresponding disaccharides are not hydrolyzed and remain in the intestinal lumen.⁷² In part, they are excreted unchanged in the feces, causing osmotic diarrhea, and in part they undergo bacterial degradation, causing fermentative diarrhea. Diarrhea is therefore the leading symptom of disaccharide malabsorption.⁷⁶⁻⁸⁰ The degree of diarrhea depends on the irritableness of the bowel and the dose of the sugar. The abdomen is distended and usually vaguely painful. The distention at first is due to liquid in the small intestine and later to gas in the colon as the sugar reaches the bacteria. Borborygmi are prominent at all levels and flatulence appears with the loose stools. The stools are liquid, foamy, and have a typical acid smell. They contain large amounts of carbohydrates and low molecular weight fatty acids, products of the bacterial degradation of the nonabsorbed disaccharides.⁸¹ Among these fatty acids, lactic acid is of special interest because it can easily be determined with chemical⁸² or enzymatic methods.⁸³ It is present in normal feces only in traces and is found in large amounts in fermentative stools.⁸¹ Steatorrhea, however, is a rare occurrence.⁸⁴

Launiala, studying human subjects,⁸⁵ found that unabsorbed disaccharide in the proximal part of the small intestine causes pronounced movement of water and electrolytes into the lumen until the contents are in osmotic equilibrium with the extracellular fluid. The unabsorbed disaccharide contributes only about a third of the osmotic activity after osmotic equilibrium is reached.

In the colon, part of the disaccharide disappears through bacterial fermentation. Although there is absorption of water and electrolytes even in relative excess of substrate disappearance, enough fluid remains to give diarrheal stools.

The diarrhea is thus due to the osmotic activity of the disaccharide in the intestine together with the organism's tendency to Na^+ -equilibrium between the intraluminal and extracellular fluids. There is no evidence to suggest that the bacterial fermentation of the disaccharide in the colon has an etiologic role in the diarrhea through decreased water absorption by the colon.

Weijers and his co-workers⁸¹ assumed that the volatile organic acids, and possibly other metabolites of the bacterial flora, irritate the intes-

tine, causing increased peristalsis, excretion of fluid and formation of mucus with subsequent diarrhea. Studies⁸⁶ using lactic acid infused via intestinal tube have not confirmed this as a mechanism of great importance.

Clinical Syndromes

Gastrointestinal symptoms due to food intolerance represent a large heterogeneous group of disorders lumped together. True food allergy and nonspecific causes may account for a large segment of the adult syndromes, but will not be reviewed. The clinical syndromes of monosaccharide and disaccharide malabsorption recognized at the present are listed in Table 2.

A. Congenital (primary) syndromes

1. Congenital lactose malabsorption without lactosuria (Holzel syndrome).

Lactose malabsorption due to congenital deficiency of lactase I was discovered in 1959.⁸⁷ Intestinal lactase activity is about 10 percent of normal. Symptoms (vomiting, chronic diarrhea) begin within the first few days of life when milk is the infants' only nutrition. Even severely malnourished infants with lactase deficiency will be cured when lactose is eliminated from the diet.⁸⁸

2. Congenital lactose intolerance with lactosuria (Durand syndrome).

This more severe form of lactose intolerance was described in 1958.⁵ Onset of symptoms is also within the first few days of life. In addition to vomiting and chronic diarrhea, the infants present with massive lactosuria, and in the majority of cases with albuminuria, aminoaciduria and renal acidosis. Blood glucose curves after a lactose load are somewhat diminished, but do not show the flat type of curve seen in lactose malabsorption without lactosuria. Despite elimination of milk from the diet about half of the infants eventually die. Autopsy shows changes in kidney, liver and central nervous system. It has been suggested that this may be due to a deficiency of lactase II, an enzyme present within the whole cell and not localized in the brush border.⁸⁹ Intact lactose is believed to be toxic, especially on the kidneys, where it is excreted and therefore concentrated (osmotic nephrosis). Milk has to be excluded from the diet early in life before irreparable damage has occurred. The pathogenesis of this syndrome has to be further

TABLE 2.—*Disaccharide Malabsorption Syndrome*

- A. *Congenital (primary) syndrome*
 1. Congenital lactose malabsorption without lactosuria (Holzel syndrome)⁸⁷
 2. Congenital lactose intolerance with lactosuria (Durand syndrome)^{5, 90, 91}
 3. Congenital sucrose-isomaltose malabsorption⁹²⁻¹²⁷
 4. Congenital glucose-galactose malabsorption^{130, 131}
- B. *Acquired (probably primary) syndromes*
 1. Acquired lactose malabsorption in the adult¹³²⁻¹⁶⁷
- C. *Symptomatic (secondary) syndromes (all enzymes decreased)*
 1. Primary malabsorption syndromes (celiac disease,^{55, 109, 190} idiopathic sprue,^{53, 55, 173} tropical sprue)^{55, 62, 191}
 2. Secondary malabsorption syndromes (Whipple's disease,¹⁹² intestinal lymphoma,⁵⁵ intestinal lymphangiectasia,^{53, 192} abetalipoproteinemia)⁵³
 3. Blind loop syndrome⁵³
 4. Kwashiorkor¹⁹³
 5. Infectious or nonspecific diarrhea in childhood¹⁹⁷⁻²⁰⁰ (acute gastroenteritis or enterocolitis)
 6. Severe malnutrition in infancy¹⁹⁴
 7. Neomycin administration (only lactase studied)¹⁹⁵
 8. Conovid therapy¹⁹⁶
- D. *Chance combination of acquired lactase deficiency with other gastrointestinal disease*
 1. Peptic ulcer⁵⁸
 2. Partial gastrectomy²⁰¹⁻²⁰⁶
 3. Ulcerative colitis²⁰⁷⁻²¹⁰
 4. Regional enteritis^{210, 211}
 5. Irritable colon syndrome²¹²⁻²¹⁶
 6. Diverticulosis and diverticulitis of the colon²¹⁷
 7. Infectious or nonspecific diarrhea in adults⁵⁵
 8. Massive infestation with *Giardia lamblia*⁹⁶
 9. Mucoviscidosis (cystic fibrosis of the pancreas)^{218, 219}
 10. Infectious hepatitis⁵⁵
- E. *Disaccharide malabsorption with intact enzyme concentration*
 1. Extensive small bowel resection⁸⁴
 2. Physiologic diarrhea of breast-fed newborn²⁸
- F. *Suggested disease associations*⁸⁶
 1. Ulcerative colitis
 2. Regional enteritis
 3. Irritable-colon syndrome
 4. Osteoporosis

investigated, but several family studies suggest an inborn error of metabolism transmitted as an autosomal recessive trait.^{90, 91}

Berg et al⁹² reported one patient with typical

clinical signs and symptoms and lactose intolerance with normal intestinal disaccharidases at 6 and 20 weeks of age. They suggested that a defect in the gastric mucosa, allowing disaccharide absorption from the stomach, would best explain these observations.

3. Congenital malabsorption of sucrose and isomaltose.

The malabsorption of sucrose and isomaltose was first described as a simple sucrose malabsorption by Weijers et al in 1960.⁸¹ In the following years, the accompanying malabsorption of isomaltose was demonstrated by Prader's group.⁹³ Sucrase-isomaltase deficiency is an uncommon heritable disorder which has been noted mostly among children^{81, 93-120} and in only ten adults.¹²⁰⁻¹²⁷ Less than half of the reported cases have been diagnosed by enzyme assay.^{114-124, 127} Eight of the 27 well-documented cases of sucrase deficiency have been found in family clusters. The disorder is present at birth. It is characterized by the appearance of fermentative diarrhea as soon as the ingested food contains sucrose, dextrans or starch. Dextrans and starch are badly tolerated because of their isomaltose content. As long as the newborn infant is fed human milk, there are no symptoms. When cow's milk, with the addition of sucrose or a mixture of dextrans and maltose, is given, diarrhea appears and the child stops gaining weight and fails to thrive. The elimination of sucrose, dextrans and starch from the diet is regularly followed by a quick improvement. Instead of eliminating sucrose one can, with the same good result, add sucrase (invertase) to each feeding.^{81, 127}

The symptoms vary in degree from individual to individual but are usually more severe in infants and young children than in older children and adults. They are, of course, also dependent on the amount of the ingested nonabsorbable disaccharides. A few patients manifest malabsorption of fat and xylose.¹⁰⁷ This complication disappears as soon as sucrose and isomaltose are eliminated from the diet. It may be caused by the accelerated intestinal passage,⁶⁰ or by the inhibiting effect of disaccharides on fat absorption.^{128, 129} With one exception,¹⁰⁵ the intestinal mucosa was always found to be histologically normal.^{114-124, 127} In the one exception (mucosal atrophy) the histologic features reverted to normal under treatment with a sucrose-free diet.¹⁰⁵

The deficiency of more than one enzyme is un-

usual in an inborn error of metabolism. The following four explanations can be proposed:⁶⁰ The mutation may have affected a regulator gene which controls the synthesis of several enzymes; it may have affected the structural gene of a polypeptide chain which is common to several enzymes; different activities may be due to different active centers of the same enzyme molecule;¹⁰⁵ or, finally, there may be a common inhibitor of several enzymes.

There is little doubt that the disorder is hereditary. There are ten records of affected siblings¹⁰⁷ and two of consanguineous parents.^{105,120} The finding of intestinal mucosal sucrase levels in the "low normal" range in relatives of two patients¹²⁷ suggested that heterozygotic individuals might have intermediate levels of the enzyme. Six pedigrees^{119,127} indicated a recessive pattern of inheritance. The highly significant difference in the means of the sucrase-to-lactase ratios between 101 normal persons and the family members of all six probands makes a strong claim in using this ratio to identify heterozygotic carriers. The frequency of heterozygotic persons in the population sample was 8.9 percent. Assuming a representative sample and a recessive pattern of inheritance the frequency of the homozygotic deficiency state was estimated to be 0.2 percent—that is, almost half-a-million people in the United States would have sucrase deficiency.¹²⁷ Reports to date have not borne out this prediction.

4. Congenital glucose-galactose malabsorption.

This disorder, discovered in 1962¹³⁰ has so far been found in only eight cases.^{86,130,131} Symptoms are identical to the disaccharide malabsorption syndromes and start soon after birth. Tolerance tests with glucose or with galactose reveal a flat response and induce diarrhea. Because glucose is the constituent monosaccharide of all disaccharides, all disaccharide tolerance tests are also abnormal. The only tolerated carbohydrate is fructose, which renders alimentation difficult. Glucose and galactose are the only actively absorbed monosaccharides.⁷² Active absorption requires energy. It involves a carrier system and probably one or several enzymes. The exact mechanism of normal glucose-galactose active transport has not yet been elucidated⁷² and the basic defect in glucose-galactose malabsorption therefore not yet found.

B. *Acquired (probably primary) syndromes*

1. Acquired lactase deficiency in the adult.

When milk intolerance secondary to isolated lactase deficiency was first described in apparently healthy adults, it was thought to be a residual of some ill-defined, transient injury or inflammation of the gastrointestinal tract.² Then, in 1966, independent studies, in the United States¹³² and in Africa,¹⁴⁶ demonstrated a racial difference between blacks and whites in the incidence of isolated lactase deficiency. Current evidence indicates that low lactase levels are the norm in the majority of adults in most populations of the world.¹⁴³⁻¹⁶⁷ Notable exceptions¹³²⁻¹⁴² are Scandinavians and those of Northern European extraction (Table 3). Adults with low lactase levels were able to drink milk as infants. Environmental factors, such as malnutrition, parasitosis, infectious diarrhea with the resultant mucosal damage, along with decreased milk ingestion might hasten the appearance of lactose intolerance. Conversely, maintenance of an adequate nutritional status by continued milk ingestion and the avoidance of intestinal damage during early childhood might delay, for a few years, the apparent onset of inadequate lactose digestion.^{36,168,169} A few investigators^{157,163} interpret this maintenance of lactase activity for three or four years as induction of enzyme activity by the presence of substrate. In any event, at the end of the first or second decade of life, lactase levels are deficient in most members of population groups that seem to be genetically destined to low enzyme levels in adulthood.³⁶ The concept of gradual decrease in lactase activity after infancy would fit with the post-weaning lactase fall seen in most animal species.^{31,32}

Among the possible hypotheses for explaining these differences in adult lactose tolerance are that some ethnic groups have a high incidence of diseases that damage the intestinal mucosa and inhibit lactase production. Even after affected persons have recovered and are in apparent good health, the effects may remain. If this explanation is correct, group differences in lactose tolerance would reflect differences in the incidence of such diseases.¹⁷⁰

It is difficult to assess the role of disease in contributing to group differences of lactose tolerance. It is recognized that there is widespread subclinical disease of the small intestine among symptom-free and seemingly normal persons in

TABLE 3.—*Lactase Deficiency in Various Adult "Healthy" Ethnic Populations*

<i>Ethnic Group</i>	<i>Country Studied</i>	<i>No. of Subjects Studied</i>	<i>Lactase Deficient (Percent)</i>	<i>Reference</i>
Caucasians	U.S.A.	508	2-19	26,55,86,133-136
Caucasians	Australia	112	6-16	137,138
Caucasians	India	30	27	139
Swiss	Switzerland	17	6	56
English	England	67	22	140
Danes	Denmark	700	6	141
Finns	Finland	159	17	142
Italian 1st gen	U.S.A.	20	70	86
Greek Cypriots	England	17	88	140
Jews	Israel	354	61-67	143,144
Jews	U.S.A.	65	58-71	86,209
Arabs	Israel	67	80	145
Negroes	U.S.A.	107	70-73	132,133,135,136
Bantus	Uganda	52	90	146
Other Tribes	Uganda	63	44	146
Bantus	South Africa	38	90	148
Chinese	Australia, & U.S.A.	100	56-100	26,137,150-152
Indians	Australia, Canada, India	85	41-100	137,139,155,156
New Guinea	Australia	8	100	157
Thai	Thailand	140	100	159
Filipinos	U.S.A.	30	90	86
Japanese	Japan	35	97	161
Aborigines	Australia	44	79-90	162
Indian-Caucasian	Colombia	45	25-38	163
Chami Indian	Colombia	24	58	164
Puerto Rican	U.S.A.	28	21	165
Mexican-American	U.S.A.	50	70	86
American Indians	U.S.A.	3	67	135
Canadian Indians	Canada	30	63	166
Eskimos	Greenland	25	88	167
Eskimos-Dane	Greenland	7	13	167

various tropical countries, and that the intestinal mucosa of affected persons is altered in form and absorptive ability.¹⁷¹⁻¹⁷³ There must be, among the world's people, differences in the incidence of subclinical disease, as well as in the more severe clinical forms of disease that induce malabsorption. It is also reported that of all the disaccharidases, lactase is the most readily affected by damage to the intestinal mucosa and is the slowest to recover.^{91,174,175}

A second hypothesis, namely that group differences in adult lactose tolerance are genetic in origin, is supported by an overwhelming majority of researchers in the medical and related fields.^{136,140,146,149,162,173,177,181,182} Also worthy of note is the inability of other hypotheses to account for the group differences in lactose tolerance. It is difficult, for example, to conceive of an explanation other than genetic that can account so readily for the persistence of high levels of intolerance among Negroes and Orientals in the United States an environment strikingly different from those of their ancestral homelands.

Turning to more specific observations, it is

relevant that various congenital disaccharide intolerances, based on enzyme deficiencies, appear to have genetic etiological factors.^{17,56,79,87,90,91} It would thus not be surprising if the adult-acquired-form of lactose intolerance has a similar etiologic base. Evidence of a familial basis for primary adult lactose intolerance is also found in four studies carried out in Great Britain.^{140,186-188}

Also suggestive is the evidence from three widely separated parts of the world of individuals or groups of mixed parentage whose parents or parent groups have high incidences of lactose intolerance on one side, and low incidences on the other. The mixed individuals among Greenland Eskimos,¹⁶⁷ and the mixed groups—Mestizos and Antioquenos in Colombia,¹⁶³ and Iru and Hutu in East Africa—¹⁴⁶ have incidences of intolerance intermediate between parents or parent groups.

C. *Symptomatic (secondary) syndromes*

Any disease with diffuse damage to the small intestinal mucosa also damages small intestinal

disaccharidases.¹⁷³ The activities of all these enzymes are decreased in a proportionally equal degree. The normal activity ratios of 6:2:2:1 for maltase:isomaltase:sucrase:lactase are nearly preserved. Normally the diarrhea-threshold disaccharide load is six times higher for maltose and twice higher for sucrose than for lactose. Whenever enzyme activity falls for instance to 20 percent of the normal—the diarrhea-threshold is lowered correspondingly. Expressed as absolute enzyme activity, lactase is the first enzyme to reach critically low levels. For this reason, lactose malabsorption becomes most prominent clinically. Ordinary dietary loads of maltose, and in most cases of sucrose, can still be handled despite the respective partial enzyme deficiency.

All diffuse diseases of the small intestinal mucosa are characterized by diarrhea as their major symptom. The diarrhea of disaccharide malabsorption is in these cases superimposed on an already existing diarrhea and therefore masked. Besides a symptomatic improvement, a curative effect on the underlying disorder may be observed after milk elimination in some non-specific diarrheal diseases especially in children.

As most primary diarrheal diseases of the small intestine are transient in nature, the associated disaccharide intolerance is also transient. General disaccharide deficiencies have so far been observed in primary malabsorption syndromes (celiac disease^{55,189,190} idiopathic sprue^{53,55,173} and tropical sprue),^{55,62,191} Whipple's disease,¹⁹² intestinal lymphoma,⁵⁰ intestinal lymphangiectasia,^{53,192} abetalipoproteinemia,⁵³ all with associated generalized villous atrophy. Greater variation is found in the degree of villous atrophy, frequency of occurrence, and degree of disaccharidase deficiency associated with blind loop syndrome,⁵³ Kwashiorkor,¹⁹³ severe malnutrition in infancy,¹⁹⁴ Neomycin¹⁹⁵ and Conovid¹⁹⁶ therapy, and infectious or nonspecific diarrhea in childhood (acute gastroenteritis or enterocolitis).¹⁹⁷⁻²⁰⁰

It is of interest that some in this last group had normal enzyme activity on biopsy although having typical disaccharide malabsorption. Nearly all of these conditions can be treated, with subsequent return of sucrase and maltase activity to normal. In nearly half of the cases, however, lactase activity in the jejunum remains selectively and permanently deficient.⁸⁶

D. Chance combination of acquired lactase deficiency with other gastrointestinal disease

Acquired intestinal deficiency, especially acquired partial lactase deficiency or the former fructose of acquired lactose malabsorption, is very frequent among the adult population. A chance combination of pronounced or partial lactase deficiency with any other disease is therefore expected to be rather frequent. One possible reason is the increase of dietary lactose load due to the regimen prescribed by the physician for the treatment of much gastrointestinal disease. Studies show no definite increased incidence of lactase deficiency associated with peptic ulcer⁵⁸ partial gastrectomy,^{58,201-206} ulcerative colitis,²⁰⁷⁻²¹⁰ regional enteritis,^{210,211} irritable colon syndrome,²¹²⁻²¹⁶ diverticulosis or diverticulitis of the colon,²¹⁷ infectious or nonspecific diarrhea in adults,⁵⁵ massive infestation with *Giardia lamblia*,⁸⁶ mucoviscidosis (cystic fibrosis of the pancreas),^{218,219} infectious hepatitis,⁵⁵ and hypogammaglobulinemia.²²⁰ After partial gastrectomy, a more rapid intestinal transit time (dumping syndrome) may be an additional factor to that of a milk-rich diet in producing symptoms of lactose malabsorption in persons with partial lactase deficiency.

Another factor to make asymptomatic partial lactase deficiency clinically manifest is its combination with inflammatory or functional disease of the large or small bowel. In persons with partial lactase deficiency, a small amount of non-absorbed lactose reaches the colon, but this amount is not sufficient to produce diarrhea. However, when the colonic mucosa is already inflamed or irritated, the small amount of lactose may trigger diarrhea. Similarly, an inflammatory or functional disease of the small bowel with acceleration of small intestinal transit time may increase the amount of unabsorbed lactose reaching the colon sufficiently to produce diarrhea or accentuate already existing diarrhea. Partial lactase deficiency thus can become symptomatic under these conditions.

E. Disaccharide malabsorption with intact enzyme concentration

Total small bowel disaccharidase activity is not only reduced by a deficiency of disaccharidase concentration, but may be reduced due to an absolute or relative reduction of total absorbing surface.

Resection of at least two-thirds of the small bowel in an adult reduces total small bowel disaccharidase content sufficiently to produce disaccharide malabsorption despite normal enzyme concentration in the remaining small bowel.⁸⁴ Lactose malabsorption will be affected first and sucrose absorption next, for the same reasons as in cases with diffuse small intestinal mucosal damage resulting in general enzyme deficiency. In children small bowel resections of lesser extent may produce symptoms of lactose and perhaps of sucrose malabsorption, because the disaccharide load is proportionally much greater in children than in adults.

Newborns have several movements of soft and acid stools when breast-fed,^{35,60} but only one to two formed alkaline stools when given cow's milk. The lactose content in human milk is approximately 7 percent and the lactose content of cow's milk approximately 4 percent. The daily lactose load of breast-fed newborns is astonishingly high and corresponds to 200 grams of lactose or the equivalent of 5 liters of cow's milk in adults.²⁸

F. Suggested disease associations

Several diseases have been associated with lactase-deficient subjects more often than with lactase-normal subjects, suggesting a possible predisposing effect by the lactase deficiency. Ulcerative colitis, regional enteritis, irritable colon syndrome and osteoporosis are four such conditions. Also the increased incidence of colon carcinoma in Japanese and Africans that become Americanized has been observed.²²¹ Many of the lactase-deficient patients with colon carcinoma that we have studied⁸⁶ have been using milk products with varying degree of symptoms long before the carcinoma was noted. The variation in fecal bacteria reported²²² in various geographic locations might be related to the extra feeding of lactose to colon bacteria, and to the increased chronic colon disease seen among lactase-deficient subjects after they have moved to milk drinking countries.

Diagnosis

A diagnosis of disaccharide malabsorption is made only when the physician considers it in his differential diagnostic thinking. In infants and children, an evaluation for disaccharide malabsorption is indicated in every case of chronic

diarrhea. In adults, an evaluation for lactose malabsorption is indicated in every case in which there is a history of milk intolerance, and in every case of intermittent diarrhea or vague abdominal symptoms, even when the dietary history given by the patient is not suggestive of milk intolerance. The absence of consistent milk ingestion or of predisposed ethnic type is also helpful in suspecting lactase deficiency. In children and adults with chronic diarrhea of known cause, associated lactose malabsorption should be searched for.

The next step is to feed the patient 50 grams of lactose in 400 ml of water. This dose corresponds approximately to the lactose content in one liter of milk.⁶⁷ In the typical case, the full array of symptoms, including massive diarrhea, will be reproduced. When no symptoms or abdominal pains occur after the 50-gram load, the test can be repeated with 100 grams of lactose. With this dose, corresponding to 2 liters of milk, the borderline deficiency patients will also experience diarrhea.²²³

For precise diagnostic purposes, the blood glucose determinations are performed at 0, 15, 30, 60, 90 and 120 minutes during the lactose tolerance test. In most normal persons, peak glucose elevations over the fasting blood glucose level occur between 30 and 90 minutes and are in the range of 21 to 62 mg per 100 ml after 50 grams of lactose. Patients with lactase deficiency show a "flat" curve, defined as a glucose rise of less than 20 mg per 100 ml for the 50-gram dose (usual range 2 to 10 mg per 100 ml) or a glucose rise of less than 25 mg per 100 ml for the 100-gram dose⁷⁶ of lactose load (usually less than 18 mg per 100 ml). During the test, subjective symptoms are noted and fecal evacuations are collected during the first 5 hours and tested with pH paper and Clinitest. The Clinitest procedure is done just as with urine testing for reducing substance. The stools in the average case contain 2 to 4 percent reducing substance. A positive test result consists of two criteria: the flat blood glucose curve, and the induction of diarrhea with a stool pH of 6 or less and having a positive Clinitest response. This combined criteria eliminates most false positive lactose tolerance tests.⁶⁷

A new modification of the lactose tolerance test has recently been described.²²⁴ Blood galactose is determined instead of blood glucose. Ga-

lactose, which is metabolized very rapidly, is blocked by the ethanol. The variation of the usual lactose tolerance test consists in administering orally 0.5 gram of ethanol per kilogram of body weight 10 minutes before the lactose load is fed. Serum galactose rises now to between 30 and 60 mg per 100 ml in normal adults, but only to between 0.6 to 1.8 mg per 100 ml in lactase deficiency.

A ^{14}C -lactose absorption test,^{161,226} using a simple CO_2 collection apparatus, has distinguished between normal and lactase-deficient subjects. The method consists of measurement of the specific activity of $^{14}\text{CO}_2$ in the exhaled air after oral administration of 5 μCi lactose-1- ^{14}C together with carrier lactose (50 grams).

Calloway,²²⁵ using a simple hydrogen breath analysis, found a hydrogen peak 5 to 6 hours after giving a small test dose of lactose in lactase-deficient patients only. This occurred when the lactose encountered the bacteria of the colon, and the results showed excellent correlation with the lactose tolerance test. This had the advantage of giving good separation of lactase-deficient from the lactase normal persons without actually causing diarrhea.

A radiological method¹²⁵ for the diagnosis of disaccharide malabsorption has been shown to be simple and reliable. The patients were each given 4 fluid ounces (120 ml) of liquid Micropaque® barium sulphate suspension, 100 percent weight per volume, to which 25 grams of a test sugar had been added. After 60 minutes a film of the abdomen was taken with the patient supine. Other reports²²⁷⁻²³⁰ all enthusiastically endorse the extremely good correlation.

The most definitive test in the diagnostic work-up is the actual determination of the disaccharidase activities in the small bowel mucosa.⁵¹ This is not necessary for the substantiation of a clinical diagnosis which has been verified by abnormal results to the disaccharide tolerance tests and normal results to the monosaccharide tests. Any of the peroral suction biopsy instruments now in use may serve this purpose. The intestinal biopsy specimen is best obtained a few inches beyond the ligament of Treitz. Absolute values for duodenal enzyme activities cannot be compared with those in the jejunum.⁵³⁻⁵⁸ However, the ratios between the different disaccharidases are identical in the duodenum and in the remaining small intestine.^{60,61} This permits the

diagnosis of a selective enzyme deficiency even from a duodenal specimen. The sucrase to lactase ratio is usually greater than 4 to 1 in primary lactase-deficient subjects, but this ratio is not useful in secondary disaccharidase deficiency and a jejunal biopsy is required for histological and enzymatic assay.⁶¹

Treatment

Treatment of disaccharide malabsorption consists in the nearly complete elimination of the nontolerated sugar from the diet in infants and small children. In older children and adults, such strict measures are usually not necessary. Small disaccharide quantities are tolerated and reduction of the respective sugars is usually sufficient.

In lactose malabsorption the only nontolerated nutriment is milk. Disguised milk sources such as creams, ice creams and puddings must also be considered.⁸ Lactose is not destroyed by boiling. Milk powders usually have the same lactose content as ordinary milk. Fermented milk products such as yoghurt and buttermilk contain little lactose. In commercially available yoghurt, however, fermentation is stopped before lactose is completely broken down, so that lactose content varies greatly. As butter and cheeses contain very small amounts, they are usually tolerated by most patients.

In infants, human and cow's milk have to be completely eliminated. Milk is replaced by soybean milk in newborns. Enteric-coated lactase tablets are available, but acid pH renders it nearly useless. Adults usually suffer no nutritional deficiencies on milk-free diets. In infants, calcium has to be supplied as calcium gluconate and, in older children and adults, by natural calcium sources such as cheese, nuts and spinach.

Congenital sucrose-isomaltose malabsorption poses a much more difficult feeding problem. Sucrose, our common cane sugar, is contained in so many foods that eliminating it from a diet is difficult.⁸ The same applies to isomaltose, a constituent of starch and glycogen. Tolerated diets in the newborn consist of milk. Later glucose has to be added to milk instead of sucrose in formula diets. In older children the diet consists mainly of milk, meat and meat products, eggs, cheese, butter and oil and starches. Fortunately small amounts of isomaltose and sucrose are tolerated with advancing age. These tolerated amounts vary from child to child and have to be

determined empirically. Commercially available and effective sucrose^{*127} (invertase) tablets may be given with meals, at a cost of about 50 cents a day, without carbohydrate restriction.

Congenital glucose-galactose malabsorption is the most difficult feeding problem. Fructose is the only carbohydrate tolerated in this disorder. The small amounts of fructose contained in certain fruits and vegetables are insufficient as carbohydrate source. Galactose is easily avoided by the elimination of lactose—that is, milk. Glucose, however, forms part of all common disaccharides and polysaccharides in human nutrition, and all have to be completely eliminated. The only exception is inulin, which is formed of fructose. Inulin is present instead of starch in *Helianthus tuberosus*, variously called topinambour, earth apple, Canada potato, Jerusalem artichoke or tuberous sunflower.⁸ This vegetable serves as the main carbohydrate source and is fed together with the usual protein and fat sources.

In all kinds of primary diarrheal disorders of children and adults, elimination of milk should be attempted temporarily for two or three weeks. Often symptomatic improvement is noted. In smaller children additional temporary elimination of sucrose may occasionally be helpful too. When the primary diarrheal disorder is cured, milk and sucrose are again tolerated in most cases.

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*Bimycanase

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PROCEDURES FOR THERAPEUTIC ABORTION

If the patient is under 12 weeks pregnant, suction curettage is the method of choice [for therapeutic abortion]. This, you may remember, was originally introduced into this country after a series of nearly 67,000 suction curettages was reported in Czechoslovakia without a single fatality. After 12 weeks the feeling is that the patient should be allowed to go to 14 weeks; she then has enough amniotic fluid to be tapped by a transabdominal amniocentesis. A total of 100 to 200 ml of amniotic fluid is drawn off and replaced by an equal amount of 23.1 percent sodium chloride solution. These patients behave in a very admirable fashion. The lag period between the saline amniocentesis and actual expulsion of the fetus will vary from one to seven days. In our experience we have had to repeat the saline amniocentesis in three different patients. On the second time around, all three patients delivered without problem. Two retained placentas have been removed in the delivery room. Otherwise the patients deliver very quietly in bed under twilight sleep.

We have found that these patients, if they are admitted to the hospital, should be scattered throughout the entire hospital population. When they are segregated, as they originally were in Hawaii, the unit quickly gets labelled a leper's colony and is treated as such.

—ROBERT N. RUTHERFORD, M.D., Seattle
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MEDICAL STAFF CONFERENCE

Hyperuricemia—Pathogenesis and Treatment

These discussions are selected from the weekly staff conferences in the Department of Medicine, University of California, San Francisco. Taken from transcriptions, they are prepared by Drs. Sydney E. Salmon and Robert W. Schrier, Assistant Professors of Medicine, under the direction of Dr. Lloyd H. Smith, Jr., Professor of Medicine and Chairman of the Department of Medicine. Requests for reprints should be sent to the Department of Medicine, University of California, San Francisco, San Francisco, Ca. 94122.

DR. SMITH:* The topic for Medical Grand Rounds this morning is hyperuricemia, with particular emphasis on pathogenesis and treatment. The patient will be presented by Dr. Glaser.

DR. GLASER:† The patient was a 57-year-old white man who died in this hospital two years ago of chronic renal failure and Gram-negative bacteremia. He gave a strong family history of gouty arthritis, with two uncles and a grandfather having had gouty arthritis. At 15 years of age the patient noted the onset of arthritis, which went undiagnosed and untreated for many years. When he was 49 years old, his arthritis was treated for the first time with dexamethasone (Decadron®), aspirin, and codeine by his private physician.

He was first seen at this hospital in 1962 at age 52 for the chief complaint of confusion and was diagnosed as having adrenal insufficiency. At that time the diagnosis of gouty arthritis was also made on the basis of extensive tophi involving the subcutaneous tissues and virtually every peripheral joint. A draining tophus was observed on the left ear, as well as typical uric acid crystals in joint fluid. His serum uric acid was 11.2 mg per 100 ml, and he was treated with probenecid and colchicine. Between 1962 and 1969 he had multiple hospital admissions for fever

and hepatosplenomegaly, and several lymph node biopsies were done. In 1966 he was treated with allopurinol in doses of 300 to 400 mg per day. On the 400 mg dose his serum uric acid decreased to 6.6 mg per 100 ml, and some softening of the tophi was observed. Even so, during this period he developed progressive renal failure and hypertension in association with Gram-negative bacteremia which led to his death.

DR. SMITH: We are fortunate to have Dr. Hibbard Williams with us today to discuss the background, pathogenesis and treatment of hyperuricemic states.

DR. WILLIAMS:* Our subject today is "the gout." The rather devastating nature of this particular ailment was perhaps best described by Thomas Sydenham in 1683.

"The victim goes to bed and sleeps in good health. About two o'clock in the morning he is awakened by severe pain in the great toe; more rarely in the heel, ankle, or instep. This pain is like that of a dislocation, and yet the parts feel as if cold water were poured over them. Then follow chills and shivers, and a little fever. The pain, which was at first moderate, becomes more intense. With its intensity the chills and shivers increase. After a time this comes to its height, accommodating itself to the bones and ligaments of the tarsus and

*Lloyd H. Smith, Jr., M.D., Professor and Chairman, Department of Medicine.

†Joseph Glaser, M.D., Chief Resident in Medicine.

*Hibbard E. Williams, M.D., Associate Professor of Medicine; Chief of Medical Service, San Francisco General Hospital.

metatarsus. Now it is a gnawing pain and now a pressure and tightening. So exquisite and lively meanwhile is the feeling of the part affected that it cannot bear the weight of the bedclothes nor the jar of a person walking in the room. The night is passed in torture, sleeplessness, turning of the part affected and perpetual change of posture; the tossing about of the body being as incessant as the pain of the tortured joint, and being worse as the fit comes on. Hence the vain effort, by change of posture, both in the body and the limb affected, to obtain an abatement of the pain.”¹

Even today this is an extremely accurate description of the clinical syndrome of gout. The culprit in this malady is uric acid, the oxidized end product of purine metabolism in man.² Uric acid is rather poorly soluble in water to the extent of only 6.5 mg per 100 ml. It has a pKa of 5.75, the ionized species being more soluble and thus accounting for the favorable response to alkali therapy in patients excreting large amounts of uric acid. In body fluids the urate ion forms the sodium salt which is estimated to reach saturation at 6.4 mg per 100 ml of serum, a concentration very close to that of the normal serum uric acid level. It is known, however, that this compound may exist in the super-saturated state in a fairly stable form, and uric acid levels as high as 100 mg per 100 ml serum have been observed in certain myeloproliferative disorders. The miscible pool of uric acid in normal subjects is about 1200 mg, with a turnover of about 700 to 800 mg per day, of which approximately one-third is excreted by intestinal uricolysis and the remaining two-thirds by renal excretion, with approximately 300 to 500 mg of uric acid appearing in the urine per 24 hours. A specific urate binding globulin has been described, but this may represent a laboratory phenomenon since the binding seems to occur primarily at 4° C with much less binding at 37° C.

Renal Excretion of Uric Acid

The mechanisms for the renal handling of uric acid deserve comment before we go on to pathogenetic mechanisms (Chart 1). Uric acid is freely filtered by the glomerulus and between 98 percent and 100 percent is reabsorbed in the proximal renal tubule. An amount equal to 10 to 15 percent of that filtered is secreted more distally in the proximal tubule, accounting for

RENAL HANDLING OF URIC ACID

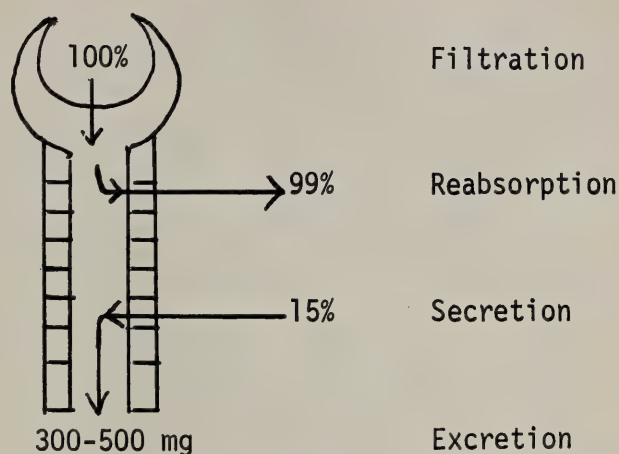


Chart 1.—Mechanisms for the renal handling of uric acid.

the daily excretion of about 300 to 500 mg of uric acid per 24 hours. A number of compounds, both drugs and organic acids, affect the renal handling of uric acid and have been of particular interest recently. Sodium and glucose both tend to inhibit the tubular reabsorption of uric acid in the proximal tubule and are thereby mildly uricosuric. The amino acid, glycine, appears to stimulate secretion of uric acid and is also uricosuric.

The cholecystographic dyes have recently been shown to be uricosuric in man, a factor which may be important in the renal toxicity of these compounds.³ A number of other drugs affect the renal handling of urate, and one of the more common ones is aspirin, which has a dual effect in this regard. In low dosage aspirin favors uric acid retention, while doses above 4 gm per day are uricosuric. In low doses inhibition of secretion alone leads to urate retention, but in high doses inhibition of both secretion and reabsorption leads to uricosuria as the effect to decrease reabsorption predominates. In fact, probably all of the uricosuric agents, such as probenecid and sulfinpyrazone, have this dual effect on the tubular handling of urate, although in doses recommended for treatment of hyperuricemia they are, of course, uricosuric.

In addition to these drugs there is a group of organic acids, particularly lactate, beta-hydroxybutyrate and acetoacetate, which inhibit urate secretion and lead to hyperuricemia. Therefore,

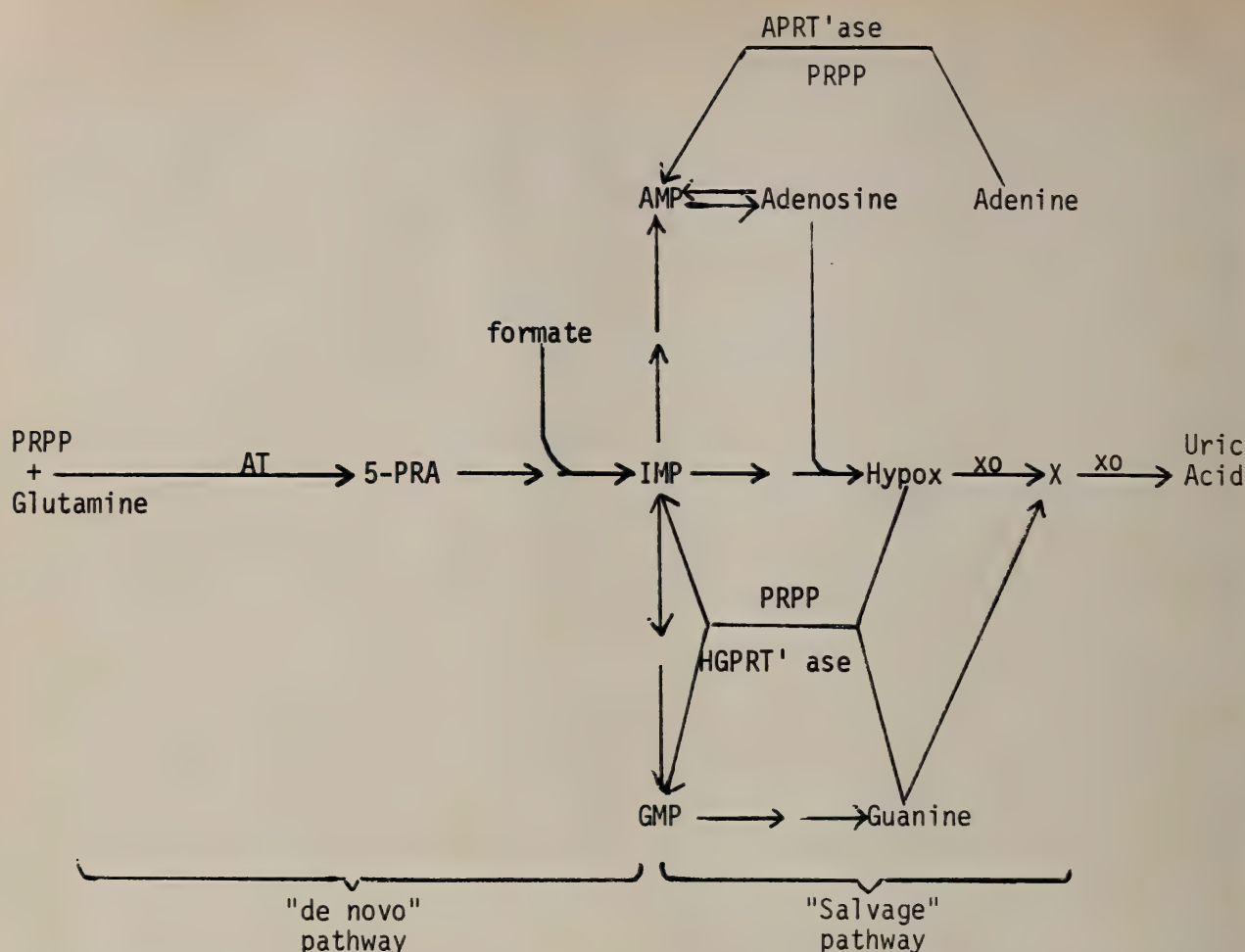


Chart 2.—Metabolic pathways in nucleotide and purine synthesis. For abbreviations see text. Additional abbreviations are: AT—amidotransferase; Hypox—hypoxanthine; X—xanthine; XO—xanthine oxidase.

any state associated with chronic lactic acidosis or the accumulation of acetoacetate and beta-hydroxybutyrate will lead to hyperuricemia, such as diabetic ketoacidosis or glycogen storage disease.

Metabolic Source of Uric Acid

The metabolism of the purine nucleotides (adenosine monophosphate and guanosine monophosphate, both essential for the normal synthesis of nucleic acids and other metabolic processes in the cell), is shown in Chart 2. As a result of the synthesis of these two purine mononucleotides, uric acid is produced as an end product, being synthesized directly from xanthine and hypoxanthine under the influence of the enzyme xanthine oxidase.⁴ Two major metabolic pathways control the synthesis of these two nucleotides, the *de novo* pathway and the salvage pathway. The *de novo* pathway begins with a reaction which uti-

lizes phosphoribosylpyrophosphate (PRPP) and glutamine to form 5-phosphoribosylamine (5-PRA). A number of subsequent metabolic steps then lead to the synthesis of the first purine nucleotide molecule, inosine monophosphate (IMP), which can in turn be converted to adenosine monophosphate (AMP) and guanosine monophosphate (GMP). The first reaction in the *de novo* pathway is rate limiting and is exquisitely sensitive to feedback inhibition by the products, GMP and AMP. In addition to this pathway and perhaps of greater quantitative significance is the salvage pathway, which converts the purines adenine, hypoxanthine and guanine to AMP, IMP and GMP respectively. Adenine phosphoribosyl transferase (APRT'ase) and hypoxanthine-guanine phosphoribosyl transferase (HGPRT'ase) are the two enzymes which control these interconversions of purines and nucleotides. Both of these enzyme systems utilize PRPP. The *de novo* path-

TABLE 1.—Pathogenetic Mechanisms in Hyperuricemia and Gout

<i>Renal—30 percent</i>	<i>Overproduction—70 percent</i>
Drugs	Idiopathic
Hypertension	Hemolytic disease
Obesity	Myeloproliferative disease
Chronic renal disease	Psoriasis (Sarcoidosis)
Lead and beryllium	Lesch-Nyhan
Alcoholism	Glycogen storage disease
Ketoacidosis	
Glycogen storage disease	
Nephrogenic diabetes insipidus	
Parathyroid disease	

way is similarly subject to feedback inhibition such that the accumulation of end products GMP, IMP and AMP will decrease their own synthesis.

Pathogenesis of Hyperuricemia

The pathogenesis of the hyperuricemic states in man is outlined in Table 1. In the clinical syndrome of gout approximately 30 to 40 percent of patients develop hyperuricemia because of some decrease in the renal excretion of uric acid and approximately 60 to 70 of patients because of overproduction of uric acid. Differentiation between these two basic mechanisms is helpful in evaluating the pathogenesis and treatment of hyperuricemia. Consideration of the syndromes associated with decreased renal excretion of uric acid involves a wide variety of conditions. A number of drugs are associated with hyperuricemia, the more important ones being aspirin, pyrazinamide and the thiazide diuretics.⁵ The thiazide diuretics have an interesting action in man. In clinical practice these diuretics frequently cause hyperuricemia, probably by inhibition of tubular secretion. However, if all of the sodium and fluid lost with the administration of these diuretics is replaced, the drug actually becomes uricosuric. The drug has a dual effect on the renal excretory mechanism for uric acid related to the total body sodium and water content. Unfortunately, the exact molecular mechanisms involved in these actions are not known. Clinically the drugs when used in the treatment of heart failure or other fluid detention states are usually associated with hyperuricemia.

Hypertension and obesity are frequently associated with hyperuricemia. This probably involves a decreased renal excretion of uric acid.

Chronic renal failure of any cause may be associated with hyperuricemia, apparently because of decreased filtration of urate. Lead and beryllium toxicity are associated with hyperuricemia apparently by inhibition of the renal secretion of uric acid. Alcoholism, diabetic ketoacidosis and glycogen storage disease, type I, are all associated with hyperuricemia on the basis of decreased renal excretion of urate as organic acids accumulate in the body. In the case of alcoholism and glycogen storage disease, the organic acid is lactate; in ketoacidosis they are beta-hydroxybutyrate and acetoacetate. Recently nephrogenic diabetes insipidus has been associated with hyperuricemia although the mechanism for this is not well understood. It appears not to be related to circulating levels of vasopressin. Both hypoparathyroid and hyperparathyroid states have been associated with hyperuricemia; again, the mechanisms have not been identified.

The overproduction mechanism accounts for a larger percentage of patients with gout, but a smaller number of specific syndromes have been identified with this mechanism.⁴ Both hemolytic disease and the myeloproliferative disorders are associated with hyperuricemia on the basis of increased nucleoprotein turnover delivering to the metabolic pool large amounts of purines which must be disposed of as uric acid. This is particularly important in the treatment of myeloproliferative diseases with chemotherapy.

Psoriasis also is associated with hyperuricemia, a finding related to the extent of the involvement of the skin. This probably is due to the increased turnover of the nucleoproteins seen with extensive psoriatic disease. An interesting clinical triad of sarcoidosis, psoriasis and gout has also been described. The Lesch-Nyhan syndrome is a very important, rare, sex-linked disorder associated with pronounced hyperuricemia and overproduction of uric acid in association with severe mental retardation, choreoathetosis and self-mutilation. This syndrome has been the focus for much of the research in hyperuricemia and gout during the last five years. For completeness, in addition to the renal mechanism, overproduction of uric acid has also been demonstrated in glycogen storage disease. Once these causes of hyperuricemia are eliminated we are left with a large group of patients who have idiopathic overproduction of uric acid. There are several

TABLE 2.—Possible Mechanisms for the Overproduction of Uric Acid in Gout

1. HGPRT'ase deficiency
Complete
Partial
2. APRT'ase deficiency
3. Abnormal PRPP amido transferase
4. Abnormal glutamine metabolism
5. Increased PRPP formation
6. Abnormal glutathione reductase

possible pathogenic mechanisms which have been studied in the last few years in an attempt to explain the overproduction in these patients (Table 2).

In the past five years the enzyme HGPRT'ase has assumed an important role in our understanding of the pathogenesis of gout (Chart 2). It was noted in 1967 that the erythrocytes and skin fibroblasts of patients with the Lesch-Nyhan syndrome lack the enzyme HGPRT'ase, thus leading to a defect in the salvage pathway of hypoxanthine and guanine conversion to IMP and GMP, respectively.⁶ Despite the fact that this disease and this enzyme defect have received a great deal of study since that period of time, we are still not absolutely certain as to the reason this enzyme defect leads to pronounced overproduction of uric acid. There are several theories which have been proposed, none of which is entirely satisfactory. A defect in this enzyme step might lead to deficient production of IMP and GMP, both of which feed back on the *de novo* pathway. Release of feedback inhibition would lead to increased *de novo* synthesis of IMP, AMP and GMP by the *de novo* pathway with subsequent overproduction of uric acid in an attempt to maintain normal intercellular levels of these nucleotides. Second, accumulation of PRPP, presumably because of failure to utilize it in the salvage pathway, may force the *de novo* pathway into greater synthesis. Third, hypoxanthine and xanthine which do accumulate in this syndrome may stimulate the amidotransferase enzyme and thereby increase *de novo* synthesis. Although the basic mechanism for increased urate synthesis is not determined as yet, the severity of the clinical syndrome and the severity of the hyperuricemia in the Lesch-Nyhan disease indicate the importance of this salvage pathway in normal nucleotide metabolism and the control of

uric acid synthesis. Recently it has been demonstrated that erythrocytes from a small group of patients with gout have a partial defect in HGPRT'ase activity. These patients are adults with overproduction hyperuricemia, gouty arthritis and a group of unusual neurological symptoms in some of the patients. Enzyme activity is approximately 5 to 10 percent of normal, and this apparently leads to the overproduction of uric acid and perhaps bears some relationship to the neurological abnormalities.

The APRT'ase enzyme, which converts adenine to AMP has been shown to be deficient in several members of a large family, none of whom had hyperuricemia or gout. However, at least one patient with a deficiency of APRT'ase has now been shown to have significant hyperuricemia and gout. In a small number of patients an abnormal PRPP amidotransferase has recently been demonstrated. The abnormality in this enzyme appears to be an inability to respond to the normal feedback inhibition by AMP and GMP, thus leading to increased production of urate by the *de novo* pathway. An increase in PRPP formation forcing synthesis by the *de novo* pathway has been described in two conditions: the hyperuricemia associated with HGPRT'ase deficiency and with glycogen storage disease. Finally, an abnormal glutathione reductase has been described in a group of patients with hyperuricemia and gout. The exact relationship of this abnormal enzyme to the hyperuricemia is not known. Despite the elegant studies which have gone into the elucidation of pathogenetic mechanisms of gout, the molecular basis for the hyperuricemia remains an enigma in most patients with this interesting disorder.

Therapeutic Considerations

Before turning to a specific consideration of modes of therapy for hyperuricemia, some comments on why and when to treat patients seems pertinent (Table 3). There are two major reasons for treating hyperuricemia: first, prevention of chronic arthritis, which can be both painful and debilitating, and, second, the prevention of chronic renal damage.⁷ The incidence of gouty arthritis seems to be related directly to both the length of time hyperuricemia is present and the absolute serum level of uric acid. The higher the serum level and the longer it is present, the more likely the patient is to develop

TABLE 3.—Outline of the Treatment of Hyperuricemia

-
- A. When and Why?
 - Prevention of arthritis
 - Prevention of renal damage
 - B. Methods
 - 1. Diet
 - 2. Alkali
 - 3. Uricosurics
 - Probenecid
 - Sulfinpyrazone
 - Benziodarone
 - (Cholecystographic dyes)
 - 4. Allopurinol
 - Efficacy
 - Complications
 - Interactions
 - 5. Colchicine
-

acute gouty arthritis. Therefore, one of the advantages of treatment is prevention of the gouty arthritis and the subsequent damage to the joints produced by this particular form of arthritis. The second reason for treating patients, prevention of chronic renal damage, is less well documented. Patients with severe chronic tophaceous gout who succumb to the disease have an incidence of severe renal damage of approximately 20 to 25 percent. What is not known is the relationship of this renal damage to the serum level or the length of time hyperuricemia is present. That is, does the patient with modest hyperuricemia of 8 to 9 mg per 100 ml damage his kidneys over a period of time without symptoms and before gouty arthritis develops? I believe the answer to this is yes, but the data is not complete enough to determine this with any certainty. Long-term prospective studies, such as those in progress at the San Francisco Kaiser Hospital by Dr. Geoffrey Fessel, are needed to determine the effect of asymptomatic hyperuricemia on renal function. However, because of this potential danger, as well as the attempt to prevent gouty arthritis, most workers in the field suggest that patients with uric acid levels persistently above a level of 9 mg per 100 ml be treated for hyperuricemia regardless of whether they have gouty arthritis or evidence of renal damage.

Forms of Therapy

What forms of therapy are available? Diet is the least effective form of therapy for hyperuricemia. If one places a patient with hyperurice-

mia on a purine-free diet, one can reduce the uric acid level approximately 0.5 to 1.0 mg per 100 ml at best. Therefore, in severe hyperuricemic states this would not be sufficient to bring the uric acid level into normal range. Excess purines in the diet should be avoided, but a purine-free diet is rarely of significant help to the patient with hyperuricemia and gout.

Systemic alkali therapy is useful in two circumstances: in the patient receiving uricosuric agents who already has pronounced overexcretion of uric acid and in the patient with a myeloproliferative disease who receives chemotherapy. Alkali should be used in this circumstance because of the tremendous load of uric acid presented to the renal tubules as increased nucleoprotein catabolism occurs.

The uricosuric agents, probenecid and sulfinpyrazone, are effective and safe methods of treatment of hyperuricemia.⁸ Probenecid has been used for nearly 20 years and has an extremely high degree of safety. Its major toxicity is gastrointestinal irritation and bleeding; there have been very few other serious side effects of therapy. For this reason, it is recommended by many physicians as the primary drug in the treatment of hyperuricemia. It may not be effective in patients with chronic renal failure, and in some patients with very large excretion of uric acid it may not add much to the already overworked renal excretory mechanisms. In addition, it poses a potential danger to the patient by increasing the uric acid concentration in the urine and thereby increasing the potential for uric acid neuropathy, although there has been little actual documentation of this potential danger.

Benziodarone is a new uricosuric agent which seems to affect primarily the renal secretion of uric acid rather than affecting primarily reabsorption as do the other uricosuric drugs. Cholecystographic dyes appear to be uricosuric, and this effect may account for the occasional renal toxicity seen after gall bladder examinations. Allopurinol, a more recently developed drug used in the treatment of hyperuricemia, is very effective in lowering serum uric acid levels by inhibiting the enzyme xanthine oxidase which catalyses the oxidation of hypoxanthine and xanthine to uric acid. Significant toxicity has been reported with the drug, namely cholestatic jaundice, skin eruptions, vasculitis and xanthine ne-

phropathy. The latter interesting complication, presenting as acute obstructive uropathy secondary to xanthine precipitation, has occurred in two circumstances: in patients with the Lesch-Nyhan syndrome treated with allopurinol and in patients with severe myeloproliferative disorders receiving both chemotherapy and allopurinol.⁹ In these latter patients allopurinol must be administered judiciously and alkali therapy must be initiated because of the accumulation of xanthine in the renal collecting system and the potential for obstructive uropathy. Finally, colchicine remains the treatment of choice for the acute attack of gout.

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102nd Annual Session of the CMA

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Second Western States Invitational Scientific Assembly

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Important Advances in Clinical Medicine

Epitomes of Progress -- Dermatology

The Scientific Board of the California Medical Association presents the following inventory of items of progress in Dermatology. Each item, in the judgment of a panel of knowledgeable physicians, has recently become reasonably firmly established, both as to scientific fact and important clinical significance. The items are presented in simple epitome and an authoritative reference, both to the item itself and to the subject as a whole, is generally given for those who may be unfamiliar with a particular item. The purpose is to assist the busy practitioner, student, research worker or scholar to stay abreast of these items of progress in Dermatology which have recently achieved a substantial degree of authoritative acceptance, whether in his own field of special interest or another.

The items of progress listed below were selected by the Advisory Panel to the Section on Dermatology of the California Medical Association and the summaries were prepared under its direction.

Reprint requests to: Division of Scientific and Educational Activities, 693 Sutter Street, San Francisco, Ca. 94102

Treatment of Superficial Malignancies With Topical 5-Fluorouracil

5-FLUOROURACIL (5FU) IS A FLUORINATED pyrimidine antimetabolite that inhibits thymidylate synthetase activity in human skin. Originally introduced for topical treatment of actinic keratoses, it has since been used to treat a variety of superficial malignant conditions of skin. Superficial basal cell carcinomas and intra-epidermal squamous cell carcinomas (Bowen's disease and erythroplasia of Queyrat) have responded favorably to 5FU treatment, although long-term followup remains uncertain as to recurrence rate. To be effective, 5FU must penetrate the full depth of tumor.

Treatment for two to four weeks with one to five percent 5FU lotion or ointment applied twice daily causes brisk inflammation, followed

by an erythematous peeling response and then clear skin. Adverse reactions include contact dermatitis, phototoxicity, and temporary accentuation of underlying cholasma and rosacea. General toxicity, such as bone marrow depression, does not occur. The efficacy of 5FU is not lost with repeated courses of treatment.

THOMAS CHAN, M.D.

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Cold Urticaria

UPON EXPOSURE TO COLD, patients with acquired cold urticaria develop hives and pruritus, and exhibit signs of systemic histamine release such as nausea, vomiting, headache, flushing, tachycardia and syncope. Application of an ice cube to skin for 2 to 3 minutes followed by re-warming usually produces a localized hive in these patients. However, some patients may have a negative ice cube test, but still develop urticaria when total body cooling occurs from exposure to cold air or water.

A personal atopic history of asthma, hayfever, or dermatitis is present in 30 to 50 percent of patients, and many have a passive transfer factor associated with IgE skin sensitizing antibodies. Cryofibrinogen, cryoglobulins, cold hemolysins, and cold agglutinins may also induce cold urticaria and should be searched for.

Treatment with antihistamines such as methdilazine (Tacaryl®) and cyproheptadine (Periactin®, Dronactin®) is helpful in some cases.

WILLIAM A. AKERS, M.D.

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The Genetics of Psoriasis

A GENETIC COMPONENT HAS LONG been suspected for psoriasis. Analysis of available data does not support an inheritance mode which is fully dominant, dominant with incomplete penetrance, double recessive, or sometimes recessive and at other times dominant with independent genes. Recent studies at Stanford University on genetic and environmental aspects of psoriasis support the hypothesis that psoriasis is compatible with multifactorial inheritance.

Mathematical models of multifactorial inheritance were employed in studying the occurrence

of psoriasis in families of 698 probands. A significantly higher frequency of the disease was found among relatives of probands than among those of controls. Pedigrees of proband families, consisting of 8,010 relatives, did not conform to any single mode of inheritance, and segregation analysis revealed frequencies of psoriasis among siblings of probands lower than expected for single gene differences.

Analysis of 125 twin pairs also indicated heredity to be a causative factor in psoriasis. Of 71 monozygotic twin pairs, 51 (72 percent) were concordant for psoriasis; of the 54 dizygotic pairs, 12 (22 percent) were concordant. The higher concordance among monozygotic pairs would lend credence that genetic determinants are operative; but the lack of 100 percent concordance for psoriasis among the monozygotics support the concept that environmental factors such as emotional stress, physical trauma to the skin, streptococcal infections, and certain drugs may also precipitate initial appearance of the lesions and recurrent exacerbation of the disease.

EUGENE M. FARBER, M.D.

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Complications of Topical Steroid Therapy

FLUORINATED CORTICOSTEROIDS ARE much more effective than hydrocortisone for topical skin therapy, but have greater adverse effects. Significant systemic absorption with adrenal suppression has occurred in infants with total body steroid application and in adults covering large skin areas with plastic occlusive dressings over steroid preparations.

Percutaneous absorption of steroids is increased 10 to 100 times when applied under occlusive dressings or to intertriginous areas. Occlusive

therapy may also induce bacterial and yeast infections, miliaria, folliculitis, hypopigmentation, striae and ulcerations.

Corticosteroids should not be applied to skin ulcerations or traumatically injured skin, as they delay epidermal regeneration and suppress fibrogenesis. Long-term steroid use may also lead to thinning of skin, telangiectasia, and capillary fragility.

VICTOR S. CONSTANTINE, M.D.

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Foods and Acne

THE BASIC LESION OF ACNE vulgaris is a closed comedone or "whitehead," resulting from the combination of androgen stimulation of sebaceous glands, hyperkeratotic plugging of vellus hair follicles into which the glands empty, and bacterial conversion of sebum to irritating fatty acids. Eventual rupture of the plugged follicle produces an inflamed cyst.

The influence of foods on this process is now being questioned. Clinical tests have not substantiated any correlation between chocolate, peanut, milk or Coca-Cola® consumption and worsening of acne. No acne flares were observed in college students who daily for one week consumed either 8¼ ounces of chocolate, 4 ounces of roasted peanuts, one quart of milk, or 24 ounces of Coca-Cola®.

Special diets for teenagers may cause self-consciousness, needless self denial, and disruption of family eating habits. It now appears that such diets are unnecessary.

E. DORINDA LOEFFEL, M.D.

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Erythrohepatic Protoporphyrria

ERYTHROHEPATIC PROTOPORPHYRIA is an inborn error of porphyrin metabolism characterized by excessive protoporphyrin in erythrocytes, stools, and occasionally in plasma. Affected individuals develop photosensitivity in childhood and may have itching, burning, redness, swelling and blistering of the skin after sun exposure. The disorder is transmitted as an autosomal dominant with variable penetrance. There are many carriers and few clinically involved individuals. Often overlooked, it may be one of the most common porphyrias. Studies have shown that the liver is responsible for the majority of excessive protoporphyrin, thus the change in name from erythropoietic to erythrohepatic protoporphyrria. Liver disease may occur and fatal micro-nodular cirrhosis with massive hepatic deposits of protoporphyrin have been reported. Treatment with an oral preparation of beta-carotene has protected against the photosensitization in this disorder.

EDWARD A. SPRAGUE, M.D.

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Cutaneous Complications of Tetracycline Therapy

TETRACYCLINE THERAPY HAS long been known to cause photosensitivity, urticaria, and exanthems, and to lead to candidiasis, particularly of vulvar and perianal skin. Recently, other cutaneous effects have been noted. Various tetracyclines may cross react to produce a fixed drug eruption, consisting of an erythematous pruritic plaque which slowly hyperpigments. The glans penis seems to be a common site for such a persistent or recurring plaque.

Several tetracyclines, particularly demethyl-chlortetracycline (Declomycin®), may cause photo-onycholysis of nails, with subungual sep-

aration of nails occurring simultaneously or following a photosensitivity skin eruption. Photo-onycholysis usually involves fingernails, but may also involve sun-exposed toenails.

Superficial acneiform pustules may also be induced by tetracycline, apparently due to bacterial suppression and consequent overgrowth of the lipophilic yeast, *Pityrosporum orbiculare*, around hair follicles.

VICTOR S. CONSTANTINE, M.D.

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Sunscreens

THE IDEAL SUNSCREEN SHOULD protect against light rays of wavelengths between 2900 and 4250 Angstroms. These include short ultraviolet "sunburning" rays (2900 - 3200 Å), long ultraviolet rays (3200 - 4000 Å), and near visible rays (4000 - 4250 Å). Long ultraviolet and near visible rays not only enhance sunburn and certain inherited photosensitivity diseases, but are the primary activating rays in most acquired photosensitivity diseases.

The sunscreen that presently seems most effective for protection against short ultraviolet light is a mixture of para-aminobenzoic acid (PABA) and alcohol. It gives a sustained high degree of protection and is non-toxic, stable, and cosmetically elegant. Other popular commercial agents either fail to provide significant protection or cause undesirable toxic effects.

Protection against long ultraviolet and near visible rays requires use of broader range sunscreens such as benzophenone, red veterinary petrolatum, titanium oxide or zinc oxide. However, repeated frequent application of these agents is necessary for sustained protection.

ISAAC WILLIS, M.D.

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Dermatophyte Test Medium

DERMATOPHYTE TEST MEDIUM (DTM) is a new fungus culture agar which enables the non-mycologist to easily grow and recognize griseofulvin-sensitive superficial fungi which infect skin. The medium contains phenol red indicator which changes from yellow to red when exposed to alkaline metabolites produced by dermatophyte fungi. It also contains cyclohexamide, gentamicin sulfate, and chlortetracycline HCl to reduce growth of contaminant yeasts, bacteria and saprophytic fungi.

The initial enthusiastic reports about use of DTM have been followed by the realization that it is not as reliable as Sabouraud's antibiotic agar for isolation of monilia and dermatophyte fungi. However, DTM provides a useful screening test and will hopefully encourage the busy practitioner to do cultures of suspected cutaneous fungal infections.

PAUL H. JACOBS, M.D.

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Topical Urea

UREA IS A NONTXIC, nonallergenic substance which increases water-binding capacity of stratum corneum, yielding softness and pliability of

treated skin. Ichthyosis vulgaris and dry, elderly skin respond favorably with 10 percent to 20 percent urea in a vanishing cream base. Added to steroid cream in the same percentages, urea may help atopic dermatitis. Its antipruritic effect makes urea comforting for itchy psoriasis and early mycosis fungoides.

Urea in 30 percent to 40 percent concentrations is strongly keratolytic. Hyperkeratotic fissured palms and soles may benefit from either 40 percent urea in vanishing cream base or 30 percent aqueous urea soaks. Proteolytic debridement of leg ulcers, necrotic malignancies, and infected wounds will occur with aqueous compresses of 40 percent urea applied for thirty minutes four times daily. Rapid deodorization of such lesions results from the antibacterial properties of urea.

Commercial urea preparations currently include Carmol® cream and Aquacare® Dry Skin Cream and Lotion.

E. DORINDA LOEFFEL, M.D.

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Staphylococcal Scalded Skin Syndrome

THE SCALDED SKIN SYNDROME is a frightening condition in which skin turns red and slides off in sheets, leaving large denuded areas. The infantile and childhood form of this is now seen to be part of a spectrum of clinical entities caused by *Staphylococcus aureus*, phage group II, type 55/71.

Included are Ritter's disease of the newborn, the childhood type of Lyell's disease (toxic epidermal necrolysis), staphylococcal scarlet fever, and bullous impetigo.

Bullous impetigo is a localized form of this syndrome whereas the staphylococcal scarlet fever, which presents with the scarlatiniform eruption but lacks the tonsillitis or exanthem of

streptococcal scarlet fever, is a mild form of the syndrome which does not progress to skin separation.

The toxic epidermal necrolysis (Lyell's disease) of the adult type is a more severe, potentially fatal disease not related to staphylococcus infection, but rather is a toxic reaction to several types of drugs. In this disorder, the skin separation is subepidermal.

An animal model is now available for study of the staphylococcal syndrome.

Newborn mice infected with phage group II staphylococci or injected with cell-free filtrates of the same organism will develop typical epidermal necrolysis.

The exfoliative toxin has been identified and partially purified.

Methicillin is the treatment of choice for staphylococcal scalded skin syndrome, leading to rapid recovery within a few days. Corticosteroids are contraindicated, except in the adult toxic epidermal necrolysis.

ALVIN H. JACOBS, M.D.

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Phenolic Depigmentation of Skin

DEPIGMENTATION OF SKIN RESEMBLING vitiligo may be caused by certain phenolic compounds. In addition to hydroquinone and its monobenzyl ether, several other phenolics are now being recognized as causing depigmentation.

Patchy depigmentation of hands and forearms has been described in hospital employees working with phenolic germicidal solutions containing p-tert-butylphenol, p-tert-amylphenol, and p-tert-butylcatechol. Similar depigmentation has occurred in auto factory workers exposed to

p-tert-butylcatechol in assembly oil. Depigmentation with this chemical could be reproduced in black guinea pigs, but not in human volunteers. The postulated biochemical basis for depigmentation is competitive inhibition of tyrosinase, the enzyme which catalyzes the oxidation of tyrosine to melanin.

Depigmentation is often a distressing symptom to patient and physician alike. When it occurs on the arms and forearms, environmental phenolic contactants should be sought before the diagnosis of vitiligo is made.

ROBERT M. ADAMS, M.D.

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Preservatives as Sensitizers

TOPICAL MEDICATIONS MAY aggravate pre-existing skin problems by causing allergic contact dermatitis. Preservatives (antimicrobial agents) are now incriminated as common sensitizers, including parabens, chlorinated phenols, formaldehyde, mercurials, and quaternary ammonium compounds.

Parabens are present in many creams, lotions, dentifrices, and suppositories. They may sensitize if used repeatedly at concentrations of 0.05 percent, whereas concentrations up to 5.0 percent may be necessary to produce positive patch tests. Chlorinated phenols include hexachlorophenes, dichlorophene, chlorocresol, bithionol, and halogenated salicylanilides. They are found in soaps, lotions, creams, toothpastes, deodorants, and disinfectants, and are capable of photosensitization. Shampoos and nail hardeners often contain formaldehyde. Mercurials occur as mercury bichloride, thimerosal (Merthiolate®), and phenylmercuric acetate in cosmetic and therapeutic creams, eye drops, and contraceptive jellies. Quaternary ammonium compounds include benzalkonium (Zephiran®) and cetalkonium chlorides, found in disinfectants, cleansing solutions, ointments, and deodorants.

Determination of hidden sensitizers should be attempted with standardized, purified preserva-

tives, as patch testing with topical medications is often unrevealing due to low concentrations of the sensitizers.

E. DORINDA LOEFFEL, M.D.

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Skin Manifestations of Drug Addiction

THE CUTANEOUS SIGNS OF DRUG addition are often the first and most obvious clues to early or unsuspected drug abuse. Most commonly seen is scarring and hyperpigmentation at injection sites, usually over veins. Also frequently encountered are abscesses and necrotic ulcerations, usually following barbiturate injections. Non-pitting edema of the hands may develop due to thrombophlebitis following intravenous injections. Fibrosis of veins, keloids, and jaundice are not rare. Patients may complain of pruritus and creeping sensations after injections. Urticaria, usually localized with flare and whealing may also occur. Tattooing from soot particles on flamed needles is seen. Accidental intra-arterial injection has resulted in ischemic gangrene of distal parts. Recently a necrotizing angiitis indistinguishable from periarteritis nodosa has been reported with drug abuse.

EDWARD A. SPRAGUE, M.D.

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Aphthous Stomatitis

APHTHOUS STOMATITIS REMAINS a diagnostic and therapeutic enigma. The recurrent necrotic oral ulcerations are often confused with Herpes sim-

plex infection, Behcet's disease, viral stomatitis, and erythema multiforme. There is no diagnostic clinical test.

Aphthae begin with burning pain, followed by ulceration, edema, and inflammation. One to thirty lesions may occur. Minor aphthae are small, few, and heal within 4 to 14 days. Major aphthae are larger than 10 mm, numerous, very painful and slow to heal. They may be accompanied by severe malaise and fatigue and may cause mucosal scarring. Behcet's disease has additional symptoms of arthritis, conjunctivitis, uveitis, and genital ulcerations. In both diseases, ulcerations histologically show criteria for delayed hypersensitivity, and in aphthae the presence of *Streptococcus sanguis* is postulated to cause hypersensitivity. Trauma, foods, chemical irritants, stress and decreased premenstrual estrogen production are other possible factors.

Treatment with corticosteroids seems most effective. Topical triamcinolone in emollient dental paste (Kenalog® in Orabase®), intralesional triamcinolone, and systemic steroids may all be helpful. Topical tetracycline, either as oral suspension or 250 mg dissolved in 30 cc of water may also help. Cyclophosphamide (Cytosan®) stopped severe destructive lesions in one case. Vitamins A, B, and C are generally not helpful, and smallpox vaccination is not recommended.

ROBERT J. ROTH, D.D.S., M.D.

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Topical Vitamin A Acid

TOPICAL ADMINISTRATION OF 0.05 percent to 3.0 percent Vitamin A acid (retinoic acid) in ethanol, propylene glycol, cream or ointment vehicles

can cause clinical or microscopic desquamation of the horny layer and favorably alter several hyperkeratotic and ichthyotic dermatoses. Following treatment with Vitamin A acid, clinical improvement has occurred in many, but not all cases of lamellar ichthyosis (nonbullous congenital ichthyosiform erythroderma), psoriasis, keratoderma of the palms and soles, flat warts and Darier's disease (keratosis follicularis). Consistent therapeutic benefits have been seen in the treatment of comedones of acne vulgaris, chloracne, and aging skin. The follicular hyperkeratosis associated with keratosis pilaris is also helped.

Topical Vitamin A acid is currently available as Retin-A® (Tretinoin), a solution of 0.05 percent retinoic acid in alcohol and propylene glycol, which is approved for use in treatment of acne vulgaris.

DAVID R. HARRIS, M.D.

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Photodynamic Inactivation of Herpes Simplex Infections

TREATMENT OF RECURRENT Herpes simplex infections is generally frustrating and disappointing with symptomatic measures designed to dry up lesions and relieve pain. Treatment with repeated smallpox vaccinations and Herpes simplex vaccines have given equivocal results.

A promising new treatment involves application of 0.1 percent neutral red or .01 percent proflavine dye to the abraded base of acute vesicular lesions, followed by 15 minute irradiation with an ordinary fluorescent lamp placed four to six inches from the lesions. This treatment is repeated once within four hours. Preliminary reports indicate a marked reduction in both inten-

sity and duration of discomfort, and an apparent decrease in frequency of recurrent attacks. Best results have occurred with Herpes progenitalis. The mechanism of action probably involves combination of dye with guanine bases of viral DNA, followed by breakage of single guanine strands produced by irradiation.

The relative simplicity and efficiency of this technique make it a welcome addition to the treatment armamentarium for recurrent Herpes simplex infections.

ROBERT M. MELNIKOFF, M.D.

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Psoralens and Cutaneous Photosensitization

NATURAL PSORALENS, FROM SEEDS and fruit, have been used since 1400 B.C. for the repigmentation of vitiligo. Two psoralens, 8-methoxypsoralen (methoxsalen) and 4, 5, 8-trimethyl psoralen

(trioxsalen), are used clinically to treat vitiligo and to increase cutaneous tolerance to solar radiation.

Psoralens stimulate pigmentation by inducing photosensitization in the presence of long-wave ultraviolet light (320-400 nm). Photoaddition of psoralen with epidermal DNA appears to be responsible for the photosensitization. A heightened but delayed sunburn reaction occurs 20 hours after exposure to appropriate wavelengths of ultraviolet light. Pigmentation subsequent to psoralen photosensitization involves an increased production of the suntan pigment, melanin, and an increase in the number of melanin-producing melanocytes in the skin.

There are no reported adverse systemic reactions. Care must be taken to avoid overexposure and severe sunburn.

FAYE D. ARUNDEL, M.D., F.R.C.P. (C)

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University of California, Los Angeles

A Time for Renewal

WE WELCOME THE American Medical Association to San Francisco and to California for what could turn out to be one of the most significant meetings of its history. Within the last year Dr. Wesley W. Hall has taken note of the widespread dissatisfaction both within and outside the profession with the performance of the AMA and has voiced the suggestion that there be a constitutional convention to consider a fundamental restructuring of the organization. At this meeting there will be hearings on this proposal and much will depend upon their outcome. For this reason this meeting of the AMA in San Francisco could not only be significant but even historic.

It will serve no useful purpose to review the evidence of public and professional dissatisfaction. Suffice it to say this dissatisfaction has existed for some time and has been frustrating to all concerned. Furthermore it tends to feed upon itself, since when public and professional support of the AMA become lessened because of it, the organization's effectiveness then becomes further reduced, and dissatisfaction consequently increases. This has been occurring much more than is healthy for either the American public or American medicine. The problem is serious because there really is no other place to turn for either the public or the profession. No other group than organized medicine can ever really be physician to society as a whole although there are a number who are at present trying to be this. And no alternative group or organization can ever really represent physicians as a whole in their professional interests and social responsibilities, unless such an organization were actually

to take the place of the AMA. This alternative would be costly and wasteful, and should not be necessary.

If it can be said that it is the function of the AMA to represent the physicians of America at the national level, just what does "represent" mean? To some, both within and outside the profession, it means the AMA is primarily a physician's protective association, and depending upon whether one is outside or in the profession one is apt to say it has been successful or unsuccessful. But to others, and it is hoped that this is the vast majority, "represent" means that the AMA will perform the essential functions of the physician at the national level in both the professional and public domain, these functions being much the same as they are in professional practice. The Sixth Progress Report of the CMA Committee on The Role of Medicine in Society attempts to spell out these essential functions in professional practice.* They may be viewed as a point of departure for consideration of the essential functions of organized medicine "representing" the member physician at the local, state and national level.

It is now essential that renewal be accomplished within the AMA for the good of both the public and the profession. There must be reassessment, innovation and fundamental change within the organization if it is to regain effectiveness in this period of scientific and social evolution which is almost revolutionary in its pace. That which experience has proved to be both good and timeless must be preserved, but there must be a far more sensitive, sophisticated and ready response to the present, and a far stronger organizational base for an effective and leading role in the future.

How is this to be done? It is suggested that the concept of a resolution oriented organization

* The essential functions are as follows:

(1) The physician gives a professional opinion or judgment based upon his knowledge, experience and expertise with respect to health and its derangements.

(2) The physician is an essential participant in all the decision-making processes throughout the whole spectrum of health care because of knowledge of health and its derangements, and of health care.

(3) The physician performs certain professional procedures and services in health care, and plays certain roles for which he must have practice skills.

with a power structure fitted more to the needs of an honorary professional society a half century or more ago, be replaced by a concept of an action oriented association to be designed to meet the needs of the profession and the public in the remaining decades of the present century. It seems obvious that the essential functions of the physician must now become the organizational functions of the AMA. If this can be agreed upon in principle, it can serve as the basis upon which to develop the specifics of a new organizational framework with an appropriate representation and power structure. This should serve both the profession and the public well and it would probably take a good deal of preliminary planning and then a constitutional convention to bring it off.

Again, we welcome the AMA to California at this very critical moment in the history of American medicine. We hope that some crucial decisions which are long overdue will be made at this meeting, and that the spirit and vitality of the Western frontier will in some fashion contribute to them. The public and the profession both need a strong, effective and responsive AMA as never before.

—MSMW

The Zollinger-Ellison Syndrome

IN 1955 Drs. ROBERT ZOLLINGER and Edwin Ellison recognized and described the classic triad which bears their names. This clinical syndrome, now familiar to almost all physicians, is that of severe ulcer disease involving the upper gastrointestinal tract, extremely high rates of gastric acid secretion, and non-beta pancreatic islet cell tumors. Not only did Drs. Zollinger and Ellison identify this clinical constellation but, demonstrating extraordinary perspicuity, suggested that the devastating hypersecretory ulcer disease in these patients was due to the liberation of a material from these tumors which stimulated the observed high rates of gastric acid secretion.

Their suspicion was confirmed by subsequent observations of others who demonstrated the presence of a gastric acid secretagogue in extracts from tumors of the Zollinger-Ellison variety.

Virtually from the recognition of this acid-promoting material in tumors, and also in blood, from patients with the Zollinger-Ellison syndrome, it was suspected, because of the characteristics of its biological activity, that this material was gastrin. It has now been established, both by chemical and radioimmunoassay methods, beyond reasonable doubt, that indeed the Zollinger-Ellison syndrome results from high levels of circulating gastrin released from gastrin-containing non-beta islet cell tumors. The development of radioimmunoassay, which permits the sensitive and specific measurement of serum gastrin concentrations, has provided clinicians with an accurate method for identifying patients with the Zollinger-Ellison syndrome.

Although extremely high rates of gastric secretion are usually found in the Zollinger-Ellison syndrome, as indicated by Dr. Sanchez and his colleagues in their article printed elsewhere in this issue of CALIFORNIA MEDICINE, gastric acid hypersecretion is by no means invariable in patients with Zollinger-Ellison tumors. Some patients with the Zollinger-Ellison syndrome may have gastric acid secretory rates which are in normal ranges, or no higher than those of many patients with more common duodenal ulcer disease. Although providing some diagnostic advantage, the ratio of stimulated to basal gastric acid secretion does not provide an adequate diagnostic method for identifying those patients with severe ulcer disease who indeed have the Zollinger-Ellison syndrome.

On the other hand, as appropriately emphasized by Dr. Sanchez and his colleagues, measurement of fasting serum gastrin levels by radioimmunoassay can be used to establish the diagnosis of the Zollinger-Ellison syndrome with confidence. Normal persons have fasting serum gastrin concentrations which are almost always less than 200 picograms per milliliter, with averages in the 50 to 80 pg/ml range. Patients with Zollinger-Ellison tumors usually have fasting serum gastrin concentrations which exceed 600 pg/ml and may be as high as 300,000 pg/ml.

It is important to identify those patients with ulcer disease who do have the Zollinger-Ellison syndrome and to distinguish them from those

having more common types of peptic ulcer disease. It is now apparent that medical and surgical therapeutic methods, which are usually successful in the treatment of common varieties of peptic ulcer disease, are only transiently effective, or totally ineffective in patients with tumors of the Zollinger-Ellison variety.

Most interesting relationships have been identified between hyperparathyroidism, hypercalcemia and the Zollinger-Ellison syndrome. It has now been well established that many patients with Zollinger-Ellison tumors, perhaps as many as 30 to 40 percent, also have hyperparathyroidism due to parathyroid adenomas, carcinoma, or hyperplasia. This association emphasizes the importance of the suggestion by Dr. Sanchez and his associates that serum gastrin measurements be performed in patients with hypercalcemia and peptic ulcer disease: this group represents a population in whom a substantial number will be found to have Zollinger-Ellison tumors. Further relationships exist between calcium and gastrin levels in patients with Zollinger-Ellison tumors. Intravenous infusion of calcium with consequent increases in plasma calcium levels is associated with decided increases in both serum gastrin concentrations and rates of gastric hydrochloric acid secretion. The observed increases in serum gastrin and plasma calcium concentrations are greater than those produced in normal persons or in patients with more common ulcer disease. It appears likely that under these circumstances elevations in plasma calcium produce increases of rate of gastrin release from the tumors, accounting for the increases in gastric acid secretion.

The case histories of the patients studied by Dr. Sanchez and his associates provide many important object lessons concerning the Zollinger-Ellison syndrome. They stress for us the variability in rates of gastric acid secretion and emphasize the fact that we cannot totally rely on this observation for the establishment of the diagnosis of the Zollinger-Ellison syndrome. They also clearly point out the curative nature of total gastrectomy in patients with Zollinger-Ellison tumors. Lesser surgical procedures performed on the stomach of patients with the Zollinger-Ellison syndrome, if tumor remains, are doomed to failure. This is borne out in one of the patients presented in this report, in whom at operation a 2-centimeter gastric cuff was per-

mitted to remain, but even this amount of residual gastric mucosa was sufficient to provide enough acid secretion to cause severe recurrent ulceration.

In histological appearance and in biological behavior, tumors of the Zollinger-Ellison variety may be benign or malignant. In these tumors there is frequently a lack of correlation between histological appearance and biological behavior. It must be emphasized that the major threat to life and to well-being in patients with the Zollinger-Ellison syndrome is usually not that of tumor invasion or metastasis but the threat is rather that of the devastating pathophysiological effects of acid hypersecretion resulting from excessive circulating gastrin. Following total gastrectomy which has cured their ulcer disease, patients with metastatic Zollinger-Ellison tumors may live many years in excellent health.

Why should gastrin-containing and releasing tumors arise in the pancreas? This question has perplexed many investigators directing their attention to the study of the Zollinger-Ellison syndrome. As is now well known, the mucosa of the antrum of the stomach, not the pancreas, is the major residence of the hormone gastrin. Attempts to demonstrate gastrin activity in normal pancreas have met with no success. Recently, however, it has been possible to demonstrate the presence of gastrin in normal human pancreas: using immunofluorescent techniques gastrin has been shown to be present in or on granules contained in the cytoplasm of delta cells in normal human pancreatic islets. Thus it appears probable that tumors of the Zollinger-Ellison variety arise from pancreatic delta cells or related cells in the pancreas.

The heterogeneity of clinical features in patients with Zollinger-Ellison tumors has been amply demonstrated by the case histories of the patients presented by Dr. Sanchez and his colleagues. As indicated by these investigators, the study of these patients attests the difficulty in establishing the diagnosis of the Zollinger-Ellison syndrome by dependency on gastric acid secretory data and establishes the value of fasting serum gastrin determinations in identifying the patients who have this potentially lethal, but usually curable, acid-peptic diathesis.

JAMES E. MCGUIGAN, M.D.

*Professor of Medicine
Chief, Division of Gastroenterology
University of Florida College of Medicine
Gainesville*

Intestinal Disaccharidase Deficiencies – Implication For the '70s

DR. HERBER HAS PROVIDED elsewhere in these pages a comprehensive review of the intestinal disaccharidases and the syndrome of intolerance to disaccharides that occurs when these intestinal surface enzymes are depressed.

After the initial surge of publications on disaccharidase deficiency in the literature during the last ten years, physicians have undoubtedly become wary of the seeming repetition and are even uncertain whether these entities have any real importance in the average physician's practice. Now we can settle down to the more mature second ten years of the disaccharidase deficiency syndromes.

Whatever the cause of intestinal lactase deficiency, it is extremely common in adults of all racial groups since the prevalence ranges from 80 to 100 percent in American blacks, African Bantus, and Orientals to between 5 and 20 percent in whites of northern European ancestry. Yet these prevalence rates do not seem to be matched by the expected plethora of patients complaining of milk intolerance, probably because they stopped drinking milk long ago for reasons no longer remembered. Who, then, should be evaluated for possible lactase deficiency? Certainly not those who no longer ingest milk and hence are asymptomatic. There are a few adults who, not realizing the association of abdominal symptoms and diarrhea with milk ingestion, become classified imprecisely as having an "irritable bowel" or the "irritable colon syndrome." Some (10 to 20 percent) of these patients can obtain complete relief of symptoms by eliminating milk products from the diet and are presumably lactase deficient. In such patients, an attempt should be made to document lactose intolerance due to lactase deficiency. This can be done by use of the lactose tolerance test with observation of the patient for typical symptoms of abdominal

fullness and diarrhea over a two-hour period after ingestion. If any malabsorption is suspected because of unexplained hyperphagia or weight loss, biopsy and x-ray studies of the small intestine are also indicated. The bulk of the biopsy specimen should be studied histologically but a small wedge (3 mg) can be wrapped in aluminum foil or paraffin sheets (Parafilm, Marathon Products, Neenah, Wisc.) and frozen for future assay. If assays cannot be carried out in a local laboratory, packing in a 1 or 2 quart styrofoam container filled with dry ice will preserve the specimen for shipping to an appropriate laboratory.

In these special circumstances, long-term withdrawal of milk products should be supported by documentation of the intolerance to lactose because empirical removal of milk from the diet may be temporarily effective merely due to the physician's power of suggestion. By carefully selecting the symptomatic patient for evaluation, we now have the capacity to establish the diagnosis of intestinal lactase deficiency and to provide long-term rational care for those afflicted.

GARY M. GRAY, M.D.

*Division of Gastroenterology
Stanford University School of Medicine*

Getting Quality into Place

THERE HAS BEEN MUCH loose talk about quality in medical care and health care. The term *quality* defies clear definition or description. Webster says "degree of fineness," a phrase which certainly lacks precision. Yet it suggests something inherent in whatever it is that has quality, an object or a service for example, which can be measured against some kind of a scale or value. In medical care and health care the quality or degree of fineness have so far eluded anything like accurate description or definition, let alone accurate measurement in terms of value against a scale of benefit accrued. The present danger is that arbitrary definitions and descriptions and arbitrary measurements of quality will come into general and widespread use to meet the practical economic needs of a sorely tested health care system, but which may have little if any true re-

lationship to the intrinsic fineness of the product or service or its value to the persons who are served.

The development of standards of quality to serve the economic needs of the health care system is already well under way. Since the costs of medical and health care services are largely paid for by the system, whether one speaks of the public or private sector, the system needs some evaluation of the worth of what is being paid for. The variables to be considered appear to be intrinsic "fineness," cost in terms of the "degree" of fineness which is necessary, and the benefits actually accrued whether these be to a patient, to a particular segment of a community or to the system itself.

The economic pressures in health care are already enormous and they are certain to become even greater. And it will be of ever increasing importance that value be received for dollars spent. The question of who will decide what quality of care will be needed in which circumstance, and how this quality will be defined and assessed is therefore in urgent need of answer. It seems likely that there is more to it than accreditation, certification, peer review and continuing education can solve, fundamentally important though each of these admittedly is. Much more needs to be done to define, describe and assess intrinsic "fineness" throughout the whole spectrum of medical and health care, and medicine

would appear to have the major professional responsibility for this, no doubt with the help of others. The relationships of the "degree of fineness" of the product or service to the need of a patient or a community would appear to be a responsibility more broadly shared between medicine and those who are to be served by the product or service. And finally the costs of whatever quality of services are needed would appear to be a responsibility further shared among the medical profession, those who receive the services, and those who must pay at least the major expense of them.

Thus, as we look down the road ahead and see that cost and cost controls are all too likely soon to become the overriding factor in medical and health care, it is not too early to begin to get quality into place. A strong beginning has been made and the tools of professional accreditation, certification, peer review and continuing education will surely be useful and can be developed further. But the role of medicine in defining, describing and assessing the "intrinsic fineness" and in relating the degree of this to cost and benefit must be extended substantially, and the quality of care for which payment is to be made must be determined in a closer collaboration among medicine, those who are to receive the services and those who must pay for them. It is becoming essential that we get quality into place and do so soon.

EMERGENCY FLUID THERAPY

I am completely opposed to the use of high-protein, high amino acid mixtures or fat mixtures or very high caloric mixtures in urgent or emergency fluid therapy. The only kind of nutrition that is necessary is approximately 100 grams of carbohydrate in a 24-hour period to cut down the adverse effects of total caloric deficit or semistarvation. Other nutrition is absolutely not necessary. In fact, if you give nitrogen in the form of amino acids the only thing you will be doing is making more urea, causing more acidosis. You will not be helping the patient during the emergency period. It's only in late convalescence that liberal caloric fat and protein nutrition has its place.

—CHARLES R. KLEEMAN, M.D., Los Angeles
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A State Medical Association on the Move

Part III: Goal-Directed Growth

ROBERT L. THOMAS,
Executive Director, California Medical Association

LIKE TODAY'S JUMBO JET LINERS, the state medical association of the seventies must have a carefully plotted course if it is to fulfill its multiple missions. With a skilled crew and sufficient fuel, both a jet and an association can get off the ground, but they run a high risk of losing their way in the turbulence unless a series of specific destinations has been scheduled in advance.

Medicine in California has always had a *basic* guidance system, spelled out in the California Medical Association's constitutional purpose established in 1856:

"To promote the science and art of medicine, the protection of the public health, and the betterment of the medical profession."

In recent years, however, California's medical leadership has identified a growing necessity to set specific guidelines for channeling the Association's resources and activities into well-defined areas of long-term commitment. Inevitably, crises of the moment affect the emphasis of the Association, but long-term goals ultimately keep the Association on its chosen course as well as reduce the number of crises.

CMA's current activities are increasingly geared to contribute directly to the fulfillment of seven basic goals:

- To improve the quality of health care and services.
- To expand the delivery and accessibility of medical and health care programs.

The first article, *A State Medical Association on the Move*, on the progress of the California Medical Association, appeared in CALIF MED 108:464-468, June 1968; *Part II: Pioneers in Planning*, appeared in CALIF MED 110:507-511, June 1969.

Reprint requests to: Office of the Executive Director, California Medical Association, 693 Sutter Street, San Francisco, Ca. 94102.

- To present Medicine's interest to government and other organizations.
- To strengthen CMA and its component medical societies as a statewide organization.
- To develop better informed public attitudes toward physicians and organized medicine.
- To improve the public's health knowledge and practices.
- To expand direct member services.

CMA is currently involved in the painful process of formalizing objectives and program priorities in relation to these goals. If an Association's program planning is to be successful, it must involve the greatest possible proportion of the membership. CMA Officers and Councilors, members of the House of Delegates, county society leaders and some 1,000 Commission and Committee members are the active program planners who are vigorously pursuing their continuing responsibility of seeing that the organization is fulfilling the needs of its membership in relation to a changing society.

Where does the organization now stand in relation to its seven basic goals? I believe that even a brief review of the way in which CMA is currently channeling its resources into identified areas of priority concern demonstrates the Association's potential for even greater goal-oriented growth throughout the challenging years ahead.

GOAL: To Improve the Quality of Health Care and Services

Statewide Peer Review Organization

It is only through well-documented performance that physicians can prove to society that

quality medical care rests in a foundation of professional self-evaluation. CMA's number one priority is the implementation of a Statewide Peer Review Organization to coordinate, enhance and publicize the excellent local peer review programs throughout the state. Specifically, the statewide organization will utilize the historic peer review experience of California physicians in developing guidelines for all medical care review functions and make such guidelines available to all component medical societies, which can then use the ranges of criteria within the guidelines in their respective review processes. The information resulting from uniform collection of data with computerized analysis will also be of great assistance to CMA's expanding programs of continuing medical education—a fundamental objective of peer review. CMA's peer review efforts are being closely coordinated with its other major thrusts toward assurance of quality care: continuing medical education and medical staff surveys.

Continuing Medical Education

Since 1934, CMA has sponsored its own postgraduate education programs to keep physicians up to date. These and other programs are now responsible for nearly 50,000 hours of instruction yearly. For many years, CMA has served as a statewide center for coordinating and publicizing of postgraduate medical education sponsored by all participating organizations—hospitals, medical schools, etc. In 1970, CMA officially launched a program to certify physicians' accomplishments in postgraduate education and to accredit these and other learning activities. Over 6,000 physicians have begun participation in this voluntary certification program, and many hospitals in California are now requiring participation in the program for renewal of staff privileges. More than 300 community hospitals and other organizations have applied for CMA accreditation of their continuing medical education programs and activities. These accomplishments demonstrate the commitment of California's physicians to high quality of patient care through their own continuing study. CMA's Certification Program lodges within the medical profession, rather than in other hands, the task of assessing the adequacy of the continuing medical education of California's physicians.

CALIFORNIA MEDICINE, the official journal of the Association, is certainly a unique CMA contribution to continuing education of physicians—as scientists, as practitioners and as leaders in the social and economic aspects of medicine and health care. This publication continues to grow in stature and influence.

Medical Staff and Long-Term Care Surveys

Because CMA believes that communities ought to be assured that their local hospital medical staffs receive continuous review by practicing physicians, it became the first medical association in the nation to formalize a plan for medical self-government and self-evaluation. Through the program, practicing physicians from CMA's Medical Staff Survey Teams join local community physicians to evaluate the care rendered and reviewed by hospital medical staffs. The California Hospital Association made the survey a provision of membership in 1969; since its inception 11 years ago, the program has surveyed more than 650 hospitals.

CMA is currently embarking on a program of review to inspect the quality of care in nursing homes. In preparation for this expansion of the survey concept, the Association developed "Long-Term Care Review—A Statement of Principles," which is a corollary document to CMA's "Guiding Principles for Physician-Hospital Relationships"—now a national standard in its field.

GOAL: To Expand the Delivery and Accessibility of Medical and Health Care Programs

CMA sees this Goal as one of the most critical responsibilities facing organized medicine and is taking steps to intensify the involvement of California physicians in movements to improve health care delivery in disadvantaged areas. For example, a CMA consultation service was recently formalized to help identify and solve problems relating to the accessibility of care in both urban and rural areas. The service stimulates county societies to identify gaps in their areas' health care delivery systems and helps them to develop realistic and constructive solutions to these shortcomings.

Through the California Medical Education and Research Foundation (CMERF), a non-profit corporation supported by CMA, the Association is

able to provide financial assistance for innovative medical care programs in their early phases of development at the local level.

In addition, CMERF is often called upon to help component medical societies in developing grant applications for funds from private and public sources. During the past year, CMERF provided assistance to ten component societies seeking funds for a variety of purposes, including financing programs of health insurance for migratory workers and evaluating the effectiveness of neighborhood health centers.

One of CMA's major roles is to evaluate the strengths and weaknesses of current and emerging health care delivery systems. The Association continues to apply carefully developed criteria regarding organization and delivery of patient care to existing programs as well as to new proposals for state and national health care. Every effort is made to see that such programs and proposals are modified to be consistent with the provision of quality patient care. The Health Maintenance Organization concept, for example, has been a subject of intense scrutiny by CMA—not only because of its potential pitfalls, but because the rapid advent of HMO's may obscure the real question of what is the best way to meet the health care needs of a given population. Countless written and personal CMA contacts with state and national legislators as well as agency personnel are devoted to presenting the concerns and convictions of California's physicians regarding the pro's and con's of the host of current proposals for health care delivery and financing.

GOAL: To Present Medicine's Interest To Government and Other Organizations

State Governmental Relations

In recent years, CMA participation in the legislative process has dramatically expanded, as has its involvement with state agencies. In all its dealings with proposed legislation, whether initiated by itself or others, the basic test applied by CMA is simply: "Is it good for the patient?" If the answer is "yes," then CMA supports. CMA's batting average speaks for itself. Of the 80 bills supported by CMA in 1971, over 75 percent were enacted; four of these were CMA-introduced bills. Of 50 bills opposed by CMA, all

but one were defeated or favorably amended. Major areas of concern were professional liability, health manpower, Medi-Cal, quackery, family planning, comprehensive health planning and public health.

At the same time as the Association actively follows some 200 bills per year, it maintains close contact with key members of the Administration, including day-to-day liaison regarding state regulations affecting patient care with the Departments of Health Care Services, Public Health, Mental Hygiene, Consumer Affairs, Welfare and Rehabilitation.

Federal Governmental Relations

One particular area which is receiving the highest priority is strengthening CMA's involvement at the federal governmental level—based on the premise that the expanding influence of federal proposals and programs on the practice of individual physicians must be dealt with at its sources in Washington, D.C. During 1971 CMA: conducted its annual visit to Washington, where our physician leaders personally met with nearly the entire California Congressional Delegation to keep them apprised of the Association's views on pending or proposed legislation; sponsored the first annual CMA Administrative Assistants' Conference on Federal Health Legislation; had periodic visits with key Congressional committee chairmen, such as House Ways and Means Committee Chairman Wilbur Mills, and numerous key HEW and Administrative officials and instituted a regular flow of written information between CMA and California's Congressmen. During 1972, CMA will expand its program of federal liaison by increasing Washington visitations to ten or twelve a year.

Communication and Coordination

CMA tries to involve as many physicians as possible in its legislative decision-making process. For example: every major specialty society is asked to designate two representatives to CMA's Legislative Commission; medical executives of county societies are routinely sent status sheets and other legislative material; the legislative committee chairman of each component society receives appropriate material in advance of each Legislative Commission meeting and is encouraged to provide the commission with the society's

viewpoints on specific bills being considered; all county medical societies are invited to send a representative group to Sacramento for an orientation session conducted by CMA.

Communications with the membership as a whole concerning legislative matters is receiving special emphasis. Both state and federal legislative news is transmitted to every member every three weeks via *CMA News*. In addition, special publications designed for key physicians within the State carry more in-depth coverage of both the state and federal scene.

CMA fosters close liaison with the American Medical Association in all activities, but the federal legislative area is receiving particular attention. For instance, CMA considers two-way communications between its Committee on Federal Legislation and AMA's Council on Legislation in advance of consideration of Congressional bills to be imperative.

GOAL: To Strengthen CMA and Its Component Medical Societies As a Statewide Organization

Actually, all CMA activities should contribute to this goal, because the organization's strength lies in the extent to which it responds to the needs of its members and the public. However, many of the Association's programs can be identified as specifically directed toward building the unity and vigor of organized medicine.

Communications with the membership play a major role in strengthening the organization, and CMA's communications take many forms:

- *CMA News*—mailed every three weeks to all members, with special issues devoted to such topics of current concern as HMO's and national health insurance.

- *Medical Executives Memo*—mailed weekly to 1,800 leaders of the profession.

- *Medical Staff Bulletin*—issued as needed to every hospital administrator and chief of staff in California.

- *Socio-Economic Reports*—issued monthly to CMA leadership and on request throughout the nation. These research publications cover a variety of vital subjects related to health care and its delivery.

- *News Service*—a monthly publication to provide information on CMA activities and programs directly to editors of county society and specialty society bulletins.

- *Statewide Meetings*—in addition to CMA's Annual Session, regular Council meetings and various conferences on special issues, the Association brings together the leadership from throughout the state at an annual Conference of Component Society Officers. Also, presidents of county societies gather for informal sessions with CMA officers two or more times each year. Another important type of statewide meeting sponsored by CMA is the Medical Executives Conference. Held in conjunction with Council meetings, these sessions provide an opportunity for staff members of county societies to exchange ideas and information among themselves and with members of the CMA staff.

- *Officer Visitations*—each year CMA's president and president-elect visit the majority of California's forty medical societies to maintain two-way communications with the "grass roots." The officers are accompanied by CMA Councilors and staff field representatives, whose job it is to maintain continuous contact with county societies.

- *Councilor Newsletters*—following each meeting of the Council, many Councilors send personalized communications to a mailing list of key physicians in their areas.

- *Medical Staff Meetings*—CMA leaders are giving greater emphasis to personal appearances at medical staff meetings held in the more than 600 hospitals throughout the State—a vital route to reaching those physicians who are not actively involved in their county society activities.

CMA devotes special attention to involvement of specialty societies and academicians in its activities. Since 1968, twenty-one advisory panels, which are composed of representatives of the eight medical schools and appropriate scientific specialty societies, have been activated within the Association's Scientific Board structure. Our advisory panels now involve more than 300 physicians. The panels have brought into being a unique forum and have begun to reduce the fragmentation of the profession to a remarkable degree. Such involvement has even drawn numerous prominent academic physicians to rejoin CMA after many years of lapsed membership. Interest in CMA's advisory panel structure has been widespread. Last year the AMA announced that it will have "Advisory Councils" to each of its 23 specialty sections in operation by 1973—patterned after the California model.

Looking to the future of the organization, CMA has also made great strides in active involvement of medical students, residents and interns. Students representing each of California's medical schools participate in CMA's Committee on the Role of Medicine in Society and 38 other CMA Commissions and Committees. These students, selected by their peers at each school, also attend AMA conventions and the CMA House of Delegates. The question of student membership in CMA is on the agenda for the 1973 House of Delegates.

California residents and interns have attended regional meetings designed to initiate a dialogue between CMA as an organization and this important group of potential members, with the objective of designing a membership program to meet the specific needs of these young California physicians.

Unity within organized medicine was a subject of widespread discussion and concern in California during this past year. Acting on direction of its House of Delegates, CMA conducted an informed opinion poll of the membership on the question of "unified" vs. "separate" membership in CMA and AMA. Thousands of CMA leaders communicated with their colleagues in advance of this poll, to assure that it would be truly "informed." Of the 16,334 physicians responding to the poll, 61 percent favored unified membership in their county society, CMA and AMA. Subsequently, the 1972 CMA House of Delegates officially reaffirmed its commitment to "... the requirement of unified county, CMA and AMA membership by all California physicians in order to maintain the integrity of a proud profession of responsible citizens able and willing to resolve problems inherent in an increasingly interdependent, socialized society."

Perhaps the best statement of the issue at stake came from the floor of the 1972 CMA House, when a prominent Scientific Board delegate defined it as "... whether or not the American Medical Association and the state medical association and the county medical association are really three separate organizations or whether they are one organization with three levels of activity." Although CMA's House overwhelmingly supported the concept of one organization, the consensus of the Association's leadership is that unity and strength in organized medicine is not a fact, but a goal, which CMA must constantly strive to realize to the fullest extent.

GOAL: To Develop Better Informed Public Attitudes Toward Physicians and Organized Medicine

In addition to accelerating its ongoing efforts to inform the public of the constructive action programs of California physicians to build a healthier state, CMA has recently launched a number of innovative projects designed to increase public understanding of the goals and activities of organized medicine. Our continuous public relations efforts include an average of three press releases each week and two radio news tapes a month, public presentations by our physician leaders and day-to-day contacts with representatives of all forms of media. Among CMA's newer approaches to establishing an informed public opinion base are the following:

- *TV Newsfilms*—This exciting television effort, in which one to three-minute color action films are prepared on major health issues and CMA's involvement in them, has been extremely well received by news programmers throughout the state. To date, these monthly films have dealt with CMA's certification program in continuing medical education, migrant health care efforts, drug abuse programs, contribution to sports medicine, peer review, combating alcoholism, and emergency medical care, to name just a few subjects. Each film is distributed to some 25 television stations throughout the state and is aired by at least half of them. They are shown during prime time—either the 6:00 p.m. or 11:00 p.m. newscasts which reach 70 percent of California households having TV sets. If CMA were to purchase this time for a year, the cost would run well over \$100,000. Instead, broadcasters have picked up the films because they are newsworthy and professionally prepared.

- *Institutional Advertising* — During 1971, CMA began preparing messages on health issues—expressing CMA policy and actions—for full-page ads carried in the California editions of *Newsweek* magazine. Subject matter has included: the root causes of poor health, peer review, county medical society activities, ecology, drug abuse, venereal disease, national health insurance and quackery. To augment the impact of the *Newsweek* messages, reprints have been distributed to county medical society bulletins, the California Legislature, all members of Congress, mayors and other civic leaders and opinion-mak-

ers as well as being reprinted in CMA publications. The response thus far to these messages, especially from state and federal legislators, has been extremely favorable.

• *Radio News Service*—This recent addition to the Association's communications armamentarium gives California radio stations "no-charge" telephone access to CMA news items, features and health hints. It consists of actual taped interviews with physician experts in the fields covered which are recorded and broadcast by the stations. Based on the knowledge that we are getting an average of 65 radio station calls per week and on a postcard survey of 380 radio stations, CMA can estimate a minimum average weekly exposure of between 350,000 and 1,000,000 listeners, or an equivalent of almost \$2,000 in air time.

Through these and other communication devices, CMA is endeavoring to create real public understanding regarding the aims and actions of organized medicine.

GOAL: To Improve the Public's Health Knowledge and Practices

CMA currently has a dozen active committees whose primary thrust includes educating the public as a means of preventing illness and maintaining health. Their names encompass the most pressing health problems of our time, including drug abuse, venereal disease, traffic safety, disaster preparedness, environmental health and alcoholism. Many avenues are used by CMA to reach the public with important health information in these and other vital areas—radio, TV, news releases, the *Newsweek* messages, and CMA's pioneering public education project, "Health Tips."

Launched in 1961 with a mailing to 89 recipients, "Health Tips" articles are now distributed *on request* to more than 6,000 outlets, including national news services, such as UPI; weekly, daily, and farm newspapers; labor and employee publications; business and industrial house organs; radio and television stations; public health agencies; physicians and county societies and most important, nearly 4,000 key school personnel. County medical societies and schools—kindergarten through universities—use the materials in a variety of ways: duplication and distribution to students and parents in entire school systems; health education course syllabi; health text

books; teacher and school nurse education; and health fairs. Close to 300 different subjects have been covered by CMA "Health Tips," many of which have been translated into Spanish for California's Chicano population. Last year, a single "Health Tip" on gonorrhea generated requests for more than 50,000 copies.

GOAL: To Expand Direct Member Services

None of CMA's goals are mutually exclusive, but this final one is the broadest in the sense that all CMA activities should benefit its membership. With this particular goal constantly in mind, however, CMA can identify and improve services which *directly* benefit the individual member, as contrasted with the many Association programs which serve the profession and the public as a whole.

To assist the individual member, CMA offers or sponsors a variety of programs of economic importance to physicians:

- A flexible investment plan, which meets the requirements of the Keogh Act, with options of eight different mutual funds, an annuity plan or any combination of these.
- An outstanding new disability income program recently initiated, which provides up to \$1,500 monthly disability income payable for the insured's lifetime if totally disabled due to injury, or to age 65 for illness disability. The competitive premium rates for this vastly improved disability income protection for CMA members are guaranteed for five years.
- Continuing and extensive efforts to effect a favorable resolution to the professional liability problems which confront physicians.

Last year a new reference book, *Professional Liability . . . Selected Medical-Legal Information for Physicians*, was prepared by the Association and distributed to every member. The booklet contains background information, sample consent and release forms and letters to assist practicing physicians. A demonstration project in patient arbitration, co-sponsored by CMA and the California Hospital Association, is seeking to develop a statistically accurate evaluation of the concept of arbitration in professional liability. Initiated in 1969, the project involves nine Southern California hospitals and their medical staffs. During the past three years, CMA malpractice legislative

activity has brought about passage of more than ten important bills to help alleviate the problem. In addition, CMA conducted an actuarial analysis of the liability situation, has sponsored regional professional liability workshops, urged the AMA to develop a specific department to provide a national focus on professional liability problems and provides assistance to component societies as requested.

- Development and updating of the *Relative Value Studies*, a means of accurate communication between individual physicians and insurance carriers, providing for specific identification of medical services.

- The Physicians' Benevolence Fund, through which CMA provides short-term assistance for physicians and their families in times of economic need. The Fund also helps to support the Physicians' Home and Elizabeth Manor Sanitarium in Los Angeles. No other state medical association has provided means for similar facilities.

- CMA's Physician Placement Service, which publicizes an average of 800 openings a year in its monthly bulletin. Last year alone, 18,000 copies were mailed to physicians throughout the

nation and 170 positions were filled in California as a direct result of this service.

- CMA's field staff, whose members not only assist county societies to become more effective and stronger, but also actively seek to identify new ways in which CMA can be of more assistance to individual members.

The foregoing represents only the highlights of the goal-directed growth CMA is currently experiencing. As Executive Director of this dynamic organization, I must admit a certain amount of pride in the aims and accomplishments of CMA. The thousands of physician-hours devoted to CMA programs are resulting in healthier, safer Californians, and helping to keep our state one in which a physician can be proud to carry on the tradition of his profession. It has been said that California is leading the way for Medicine in the United States. If this is so, the credit must be divided between the progressive pioneer doctors of early California whose organizational purpose is as relevant now as it was in 1856, and the California physicians of the 20th Century, who are continuing to look toward the future with determination and strength.

NAIL CHANGES IN CHRONIC RENAL DISEASE

Fingernail changes are common in patients with chronic renal disease, and identification of these changes may help to differentiate acute from chronic renal disease. A narrow one to two mm dark band at the distal portion of the nail combined with a relative paleness to the proximal nail, as described by Terry, is common in patients with chronic renal or hepatic disease. It is not a specific sign, and there are false positives. When the dark band occupies 20 percent or more of the nail band, this is called the "half and half nail." When this is present, the patient usually has chronic renal disease. Muehrcke described the double or paired white bands in patients with hypoalbuminemia. These or a single band or line have been observed in patients with renal failure.

—CARL F. ANDERSON, M.D., Rochester, Minn.
Extracted from *Audio-Digest Internal Medicine*, Vol. 18, No. 11,
in the Audio-Digest Foundation's subscription series of tape-recorded programs. For subscription information: 1930 Wilshire Blvd., Suite 700, Los Angeles, Ca. 90057

Approaching the Time for Decision

The President and the Chairman of the Council Address Medicine's Problems

Refer to: Crum JF: CMA looks ahead: Approaching the time for decision—The hard choices facing American medicine. Calif Med 116:65-70, Jun 1972

The Hard Choices Facing American Medicine

JEAN F. CRUM, M.D.,
President, California Medical Association

THE ACHIEVEMENTS OF MEDICINE in this country have been great. Few would argue the point. But today we cannot afford the luxury of recounting past accomplishments. Rather, we must devote our energies to assessing the future—and preparing for it.

In his novel 1984, George Orwell painted a bleak picture of the future for western man—a society in which government keeps itself in power by complete control over man's actions and his thoughts. The following is from Orwell's book:

"The Ministry of Truth . . . was startlingly different from any other object in sight. It was an enormous pyramidal structure of glittering white concrete, soaring up, terrace after terrace, three hundred meters into the air. From where Winston stood it was just possible to read, picked out on its white face in elegant lettering, the three slogans of the Party:

FREEDOM IS SLAVERY
IGNORANCE IS STRENGTH . . .
WAR IS PEACE

"Ignorance is strength." That sounds like some of the bureaucratic jargon we hear today.

Address of the President: Presented at the Annual Meeting of the House of Delegates, California Medical Association, San Francisco, February 15, 1972.

Reprint requests to: Mr. David Greer, Division of Professional and Public Relations, California Medical Association, 693 Sutter Street, San Francisco, Ca. 94102.

The year 1984 is still 12 years away. But some of Orwell's predictions seem to be taking shape already. Government is playing an ever-increasing role in our everyday lives. Some segments of our society are "hooked" on drugs. Our system of free enterprise is steadily being eroded. Individual initiative has almost become old fashioned.

In many ways, we in the medical profession have been among the first to be hit by this "wave of the future." It is not necessary to recount the steady encroachments of the Federal Government on the practice of medicine. Nor is it necessary to emphasize the almost unbelievable strides taken by medical science in the recent past. We have just emerged from a decade in
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Refer to: Saidy JT: CMA looks ahead: CMA priorities and communications. Calif Med 116:65-69, Jun 1972

CMA Priorities and Communications

JOHN T. SAIDY, M.D.,
Chairman of the Council

ON FOUR PREVIOUS OCCASIONS, 1967, 1968, 1969 and 1970, the Council has presented the House of Delegates with proposed Goals and Objectives for the California Medical Association.
(Continued on next page)

Presented as a supplementary report of the Council to the California Medical Association House of Delegates, San Francisco, February 12, 1972.

Reprint requests to: Office of the Executive Director, California Medical Association, 693 Sutter Street, San Francisco, Ca. 94102.

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Hard Choices

JEAN F. CRUM, M.D.

which more and greater change has taken place than any other decade in the world's history. And even more important for us today, the decade that we have entered promises to make the past appear placid by comparison.

Society will change, regardless of our actions. Our duty—our responsibility—is to bring our energy to bear on this change, to assure that it serves the best interests of our patients and our nation. But what happens if our efforts are of no avail? What happens if government decides simply to absorb the medical profession? Have we carefully considered all of our alternatives in such an event? Clearly, we have not.

Not long ago I had an opportunity to discuss the plight of our profession in the province of Quebec with a surgeon who had witnessed the whole series of events there. He told of the frightful toll that loss of personal freedom took upon the physicians in that province. He noted that good physicians—conscientious, reputable, outstanding physicians—left Quebec during that tempestuous period. Clearly, they had not anticipated the future in time. We must learn from such experiences. We must chart the various possibilities for our future and devise well-reasoned, workable alternatives.

What would we do if we found ourselves faced with an untenable situation in which to practice medicine? Would we speak ineffectually with fragmented voices and be forced to comply, giving in meekly to government edict? Or, could we justify the effective withholding of our services—as some doctors in other countries have done? Somewhere between these two extremes must lie workable alternatives. To learn of them and to utilize them effectively, we must become thoroughly familiar with what has happened in other countries—in England, Belgium, the Scandinavian countries, in Quebec.

Does the answer lie in the adoption of the guild structure by medicine? Perhaps the whole nature of medical societies must change. We must intelligently weigh the various courses of action open to us. Should medical organizations in the future concern themselves primarily with politics, or with socio-economics, or solely with the exchange of scientific knowledge?

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Priorities and Communications

JOHN T. SAIDY, M.D.

While the goals adopted in 1970 will be reevaluated by the Council in light of attitudes expressed by the 1972 House of Delegates, we believe that in general the Association maintains its commitment to these previously stated goals.

Our particular concerns at this time are primarily those of priorities and communication.

Priorities

We believe that CMA's various programs must be subjected to intensive scrutiny from the standpoints of priority, current relevance, progress toward achievement and appropriate involvement at the proper membership level. Continual program analysis and performance review are mandatory to help us work more effectively on fewer and more significant tasks. If needs and problems determine organizational structure and not the reverse, we have a real chance to streamline the Association focusing its activities on the most important and appropriate objectives. We can then minimize unrewarding peripheral involvement in so many areas which disperse our efforts, effectiveness and funds, and are often rather unproductive in the end.

Although there may be general agreement on goals, a rational delineation of spheres of activity and the roles of the various levels of membership and leadership in CMA programs is necessary. The essential attributes of such programs are anticipation, consideration, decision and action. With proper assignment, overlapping can be minimized and more participation achieved with a better balance of effort. The template of the CMA structure may not be appropriate for county medical societies and vice versa since the degree and manner of such participation in so many activities will vary considerably.

Peer Review serves as an example of such proposed coordination. Utilizing the existing and potential activities of physicians at each level of organized medicine in California, the California Peer Review Organization was created by the California Medical Association to anticipate the increasingly important need for physician direction of all forms of Peer Review within the state.

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Should medical societies continue their attempt to combine all three? Would it be appropriate for a subsidiary organization to function wholly for the purpose of collective bargaining—having flexibility and toughness in promoting the enlightened self-interest of physicians? Solutions are not simple or easily derived. I do urge that we thoroughly consider these questions. Now.

In 1964, a long-time critic of organized medicine said: "The AMA—operating from a platform of negative vigilance—presents no solutions but busily fights each change and then loudly supports it against the next proposal." Perhaps this is the way that we are viewed by some of the American public. By how great a segment—who knows? Certainly in some minds organized medicine represents the forces of reaction in health care rather than the forces of constructive leadership.

What will happen if people of this belief—regardless of its merits—are in a majority and their opinions prevail? Do we become conformists? Or do we face a future of increasing discord and confrontation? It is essential that we find the means to establish those principles upon which we can stand. We must examine—and then reexamine—those beliefs we currently hold that may be challenged. We must know where we stand and we must be able to support our positions with strength and conviction. To prepare for a confrontation, we must be able to speak from competence. There are activities in which our participation now will undergird us for the challenges that lie ahead.

By competent self-regulation the profession may remain, in the words of Vannevar Bush, "so respected that public opinion itself will insist on its independence [in order to] maintain and enhance the characteristic which should be essential in every profession: devoted service to the people, exercised with pride and dignity."

Peer review, its continued implementation, expansion and refinement, offers us this opportunity. Peer review—that means appropriate evaluation of physicians' activities by other physicians without contractual relationship with government or other third parties. Peer review

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Priorities and Communications

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Selected for their demonstrated expertise, the physicians composing the new CMA Commission on Peer Review are developing an organization which is oriented towards the encouragement of a continuation and refinement of existing Peer Review mechanisms using a variety of local approaches to assure quality care for the public. Although all of organized medicine is involved in this critical task, implementation of a California Peer Review Organization involves specific division of functions at the local and state levels.

Physicians at the local level, through their county medical societies and with the assistance of their executive staffs, are responsible for maintaining a systematic program of review of all health care and costs in their respective areas focusing upon quality of care, utilization and charges.

California Medical Association, through its Commission on Peer Review, is responsible for the statewide administration and coordination of the California Peer Review Organization; for the development and coordination of the educational aspects of peer review; for appellate review; for research and development of regional norms; for performance evaluation of peer review mechanisms, not peer review itself; and, for assisting and encouraging local review units as requested, or as indicated.

Different levels of participation, different forms of responsibility, but a commonality of purpose make the California Peer Review Organization a unique and exciting opportunity for all, physicians and staff alike, who share medicine's commitment to better patient care.

Communications

The cliché of communications being a two-way street remains true. However, if there is any reason for intraprofessional communication it is to keep the profession alive. The same can be said for communications to the general public and to all who have assumed the burden of provision of medical care as theirs: Reiteration of goals and programs is necessary although to those now on the Council it may not seem so after the first few times. To the non-member and

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—that includes an evaluation of the propriety and effectiveness of care rendered, as well as its quality.

Our recently formed Peer Review Commission of the California Medical Association has an almost awesome responsibility. Like Caesar's wife, it must be above suspicion. It must merit the total acceptance and wholehearted cooperation of all our physician members. It must be pure, free of all financial entanglements with governmental agencies that would effect constraints against its acceptability and effectiveness. Our peer review program may incorporate these desirable qualities and also include public accountability as well.

CMA's program of Continuing Medical Education also affords the public tangible evidence of quality care. Voluntary participation by a much larger percentage of our membership is urgently indicated if this program is to serve as an effective deterrent to compulsory recertification and relicensing.

Our desire to improve upon our present system of medical care—to correct its deficiencies and build upon its strengths—is exemplified by our continuing concern for improving access, maintaining and elevating quality and controlling costs.

To add to these efforts, to counter our detractors and strengthen our position, we need to be more effective advocates for the merits inherent in the private system of medical care. In the words of Doctor Dwight Wilbur, "The voluntary association of two men, one giving and one seeking relief—this is the heart of the art of medicine." Without question, the "art" suffers irretrievably from the loss of the "heart."

Recent discriminatory price controls on physicians are onerous. While physicians properly seek fair treatment, we are a part of the body politic and must participate in the solution of national problems. We must, by self-regulation, exercise constraint on our fees or accept the risk of pricing ourselves out of freedom.

All of these programs and preparations, to be effective, must be based on a strong and unified CMA, broadly representative of all physicians in California. Unity in this context is

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JOHN T. SAIDY, M.D.

uninvolved member it also seems unnecessary but for different reasons. Those physicians who choose non-membership or non-involvement must be informed of CMA activities and their positive benefits and results for both their patients and themselves.

Council membership is in itself an intense educational experience, the results of which need to be told to the membership. The exposure to differing points of view within the profession is a salutary one resulting in increased understanding and respect for one's confreres and their ideas. In most instances, there follows a general informed consensus on courses of action which are in the best interest of the public and the profession. More important, perhaps, though less rewarding and often more traumatic in the personal sense, is the exposure to the non-medical community, which is so actively manifesting its interests in all aspects of health care. This leads to a feeling among many physicians, particularly those who are not directly involved, that there is a near national conspiracy to take the direction of health care away from the professionals. This is only partly true.

On the political front there are empty promises, grandiose plans and a harmful and disturbing evocation of false expectations. The last carries with it the implied criticism of the professionals that failure to deliver on such political promises is further proof of the need for governmental or non-professional control, the devastating consequences of which are never mentioned.

On the other hand, those who are most sanguine about the complexities of the system are strongly in favor of a pluralistic approach and the least possible governmental provision or control of services. Well aware of the cost involved and the real expectations of any system, they are particularly desirous of increased medical participation at the earliest possible moment in the design of all aspects of proposed changes. They, too, deplore the simplism of the politicians and share medicine's conviction that professional matters are not soluble by rhetoric or political means.

Medicine has this great chance, as it has always had, but because of the current political

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Hard Choices

JEAN F. CRUM, M.D.

identified as unity of purpose. Different points of view and varied approaches to problems will persist in any healthy democratic organization—and indeed they should. But differences must not be disruptive. Unity of purpose must prevail. It will result in positive achievement and progress.

You may ask, What can one person do to promote unity? I say to you that you can set an example by emphasizing the positive, look for the goals and the objectives that we have in common, and cease to dwell upon matters in which we are different. Wisdom of two centuries ago states, "If men would consider not so much wherein they differ, as wherein they agree, there would be less of uncharitableness and angry feeling in the world."

I invite each and every physician to espouse this credo and to put it to work. You are organized medicine. Its continued effectiveness, or lack thereof, depends upon your efforts.

There exists within our organization, as in many others, a dissident group. They are critical of organized medicine. They participate in its affairs dispiritedly, if at all, and base their highly vocal disagreements primarily on socio-economic grounds. They generate a remarkable volume of dissent. And they create ill-concealed satisfaction in those people who would take a meat cleaver to our present private system of medical care if they had their way.

In summary, then, we must continue in our attempts to provide effective solutions to the health care problems facing our nation. It is necessary that we—and all Americans—rethink some of our ideas about improving health care. The American public has not been made sufficiently aware that there are many other factors even more influential in a nation's health than medical care. Specifically, environmental protection and enhancement, inadequate general health education, automobile accidents and drug abuse are all factors to which our nation has devoted too little attention. Instead of making concerted efforts to attack these problems, Americans too often have fallen victim to the idea that new programs of government financing will perfect our system of health care.

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Priorities and Communications

JOHN T. SAIDY, M.D.

climate it may not have such future opportunities. Therefore, only a near-total response to the challenge will help us to preserve those elements which we know to be essential for the improved health care of the nation. This invitation is that medicine expand its social responsibility as a profession and take the lead in improving those elements of the system—quality, accessibility, availability—which will lead in Rutstein's words "to the ultimate goal of decreased disease, decreased disability, and decreased untimely death." Withdrawal or non-involvement will leave the field open for the incapable, the misinformed and the political. In Medicine's absence they will prevail; in its presence, they will fail and the entire nation will be better, not for their failure alone, but for our success. □

(Continued)

Hard Choices

JEAN F. CRUM, M.D.

Clearly, our health care problems—or any of our social problems for that matter—will not be eliminated by adding billions of dollars to public-sector spending. Unfortunately, too many of our citizens seem to equate spending money with making progress. What we need is not more dollars but better ways to use them. We need programs which are goal-oriented and which concentrate on achieving very specific, carefully defined objectives—such as offering solutions to problems like environmental pollution or inadequate housing, sanitation and nutrition. This approach might well prove to be the only really workable way to eliminate some of the deficiencies in American health care. On the other hand, there are the currently proposed legislative attempts at drastically restructuring our system of medical care. Using these, we might easily continue to pour endless billions of dollars into an indiscriminate quest for better health care—only to discover later that this goal has eluded us.

I do not have solutions to the problems that I have posed. My objective in raising them is
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Hard Choices

JEAN F. CRUM, M.D.

to indicate that the various alternatives we face must be carefully evaluated and courses of action must be developed for each contingency.

I would like to quote from a lecture delivered by a contemporary scholar. It has relevance today for us as physicians—and for us as Americans.

"There are many ways in which a nation can die. It can die from internal strife, tearing itself apart. It can die of indifference, of an unwillingness to face its problems, an incapacity to respond to the suffering of its people. Or a

nation can die of old age, not chronological so much as psychological old age—a waning of energy and an incapacity to learn new ways.

"There is no danger that we will fail to respond to the sweep of change. It forces our hand. The danger is that we will respond sluggishly. The danger is the creeping disaster that overtakes a society which little by little loses a commanding grip on its problems and its future."*

There is a Chinese imprecation that goes, "I curse you. May you live in an important age." We are living in an important age. We have hard choices ahead. Let history record that we were ready.

*John W. Gardner, The Godkin Lectures, Harvard University, 1969.

DIALYSIS UNITS—HIGH RISK AREA FOR VIRAL HEPATITIS

There are certain kinds of "critical care units" in which viral hepatitis and association with the Australia antigen have been unusually common. Dialysis units throughout the world are an example of this. In our own dialysis unit at the General Hospital here in Los Angeles, we have monitored 62 patients undergoing chronic dialysis. Forty percent have developed clinical viral hepatitis. An additional 22 percent have apparently been infected by the agent, showed no evidence of hepatitis, but began to circulate the Australia antigen.

Most impressive and what I want to emphasize is the spill-over into the personnel who have a contact with these patients. Nearly half of the nurses have developed frank hepatitis. A third of the technicians working in that unit have developed hepatitis. A tenth of the physicians, including house officers—residents who spend only a period of six weeks to two months in the unit—have developed frank icteric hepatitis. Most impressive of all is the fact that eight of the spouses of patients undergoing dialysis have developed acute viral hepatitis. They have all been the spouses of persistently antigen-positive dialysis patients.

—ALLAN G. REDEKER, M.D., Los Angeles
Extracted from *Audio-Digest Anesthesiology*, Vol. 13, No. 7, in the Audio-Digest Foundation's subscription series of tape-recorded programs. For subscription information: 1930 Wilshire Blvd., Suite 700, Los Angeles, Ca. 90057

Medical Students and Organized Medicine

GEOFFREY A. SMITH, B.A., AND JONATHAN E. MANDELBAUM, A.B., *Davis*

ACTIONS OF TODAY'S DOCTORS have consequences, good and bad, for today's medical students. Over the past three years, California medical students and physicians of the California Medical Association have worked out a model for relations between organized medicine and students.

The development of this relationship occurred on the background of social change that has characterized the last decade. Time was that medical students were accurately characterized as a hard-working, homogenous group interested in little other than text and ward medicine and having almost no time for anything else. During the sixties, the social awareness of all students, medical students among them, was heightened. The Student American Medical Association (SAMA), long the large but inactive voice of medical students, began to show concern with disfunctions of our health system, and with ways to deliver health care to the poor, the migrant, the Indian, and the Appalachian populations. Other concerns have been ecological problems, medical manpower, minority group problems, and medical politics. Members of the CMA became aware of the expanded areas of medical students' interest and recognized a need to communicate regularly with them.

The CMA set up the Committee on the Role of Medicine in Society, which included the elected leaders of the eight California medical schools and an equal number of leaders of the CMA. The committee was charged with developing a long-range health care planning report and it served as the main interface between students and physicians. The eight student members were sent as student CMA delegates (with

their eight alternates) to the annual sessions of the CMA House of Delegates. There they worked with reference committees and on the floor of the House of Delegates. At the last annual session, students developed and won the House support for a resolution recognizing the elected student representatives from each California medical school as full delegates in the CMA House of Delegates. Also, a medical student newsletter was developed and funded; and a mechanism was developed to incorporate students and house staff into the CMA. The intent? Both to increase the awareness of California medical students and to widen the base of representation by the CMA.

The Role Committee students and their alternates have also been ex-officio members of California's delegation to the AMA House of Delegates meetings. There, in addition to working on AMA's support for SAMA's MECO (Medical Education and Community Orientation) program, government support for medical students, ecology, abortion, and Cannabis legalization, students have worked toward their enfranchisement within the structure of the AMA. A main objective has been to give the elected medical student representatives full delegate privileges as leaders of a student section of AMA and, at the same time, convince the AMA that medical students should continue to have their own independent organization, The Student American Medical Association.

Since most medical students intend to become house officers, the relation of the new House Staff Organization to AMA also has been of major interest and concern. We believe that it would be best to have both a section in AMA for house staff and a separate and independent House Staff Organization.

More general and numerically greater has been student participation on CMA commit-

Fourth-year medical student, University of California, Davis, National Vice President, Student American Medical Association, and student representative on California Medical Association Committee on the Role of Medicine in Society, 1970-1972 (Smith); Second-year Medical Student, University of California, Davis, alternate student representative on California Medical Association Committee on the Role of Medicine in Society (Mandelbaum).

Reprint requests to: G. A. Smith, M.D., c/o K. Olson, 693 Sutter St., San Francisco, Ca. 94102.

tees. There, more than 40 student representatives (besides the Role Committee members) have sat and deliberated with member physicians this past year.

During the last CMA convention, resolutions were introduced asking for a candid evaluation of the effectiveness of student representatives working within the structure of organized medicine. We agree with the spirit of such resolutions and would like to take this chance to cite some examples of student contributions to the CMA. There was major student participation in the formation of the Sixth Progress Report of the Committee on the Role of Medicine in Society, "The Physician and His Practice, 1980-2000." (Calif Med 116:71-95, April 1972.) This document in all likelihood will be used as a source of information for the planning of medical student education and health care delivery systems. At the 1972 CMA convention, medical students developed and delivered a lively presentation on medical education today, including a slide show and audience participation. As a final example, medical student representatives introduced successful resolutions concerning recycling of disposable hospital supplies, incorporation of house staff and students, liberalization of current CMA positions concerning marijuana, and condemning non-ethical aspects of pharmaceutical house advertising.

What are the current weaknesses of the program? It has sometimes been difficult for the medical students to find time to participate effectively in CMA or local society activities. This will probably always be a problem, but with the new California medical student newsletter, it will be easier to become acquainted with what fellow students are doing with the

issues and activities of organized medicine. In the past, some medical school administrators have been skeptical about medical student involvement in CMA activities. Some have openly spoken out against medical student participation in any non-"academic" extracurricular activity. We hope that with time all school administrators will appreciate the value and importance of active contact between the practicing physicians and students.

With few exceptions the personal experiences of the students have been favorable. Most began their involvement with some distrust and skepticism toward CMA. They have come away with an appreciation for the complexity of the organization and the breadth of opinion contained within it. Although most found CMA to be a conservative organization, it has not been as rigid as expected. In fact many have stated they have been able to work effectively within the organization to accomplish some of their goals. Nearly all the resolutions introduced by students so far have been acted upon favorably by the CMA delegates.

In summary, the leaders of the CMA have realized that tomorrow's physicians must be more than just medical technicians and must be involved at every level of decision-making in planning and administering the health care delivery system. This was strongly emphasized in the "Role Committee" report. An awareness of what's going on politically and the knowledge of how to work effectively to enact change within the system should be an integral part of the education of a responsible physician. For an increasing number of California's medical students, CMA involvement is the essential ingredient in providing that education.

URINE OUTPUT IN GAUGING HYDRATION IN ACUTE OR EMERGENCY CARE

Remember that the hourly urine output is a vital sign in determining whether a patient is overhydrated or underhydrated. . . . In truth, any time you want to know the blood pressure, pulse, temperature, and respiration, you also want to know the hourly urine output. This means that you have to commit the patient to a Foley catheter. This is one of the things we have finally started doing.

—CHARLES D. SWARTZ, M.D., Philadelphia
Extracted from *Audio-Digest Internal Medicine*, Vol. 18, No. 11,
in the Audio-Digest Foundation's subscription series of tape-recorded programs. For subscription information: 1930 Wilshire Blvd., Suite 700, Los Angeles, Ca. 90057

Help from Helpmates

With It with the CMA Auxiliary

JANE ESHLEMAN CONANT, *San Francisco*

AT A CALIFORNIA MEDICAL ASSOCIATION convention not too long ago, one of the attending science writers observed a line of women, all nicely dressed-up and chattering a mile a minute, waiting to enter a dining room for their annual lady lunch.

In a tone that was benign and condescending and carried just a touch of male chauvinism, he remarked:

"Look at all the pretty little birds—just like a bunch of canaries."

It is time to correct the gentleman.

Chattering? Yes.

Pretty dresses? Admitted.

Lady lunch? It's true.

Canaries? No.

Canaries don't carry on projects against pollution and drug abuse. They don't collect medicines and equipment for poverty area health care. They don't train young people and senior citizens in baby-sitting, recruit volunteers to work with victims of stroke, or seek ways to educate the young about drug abuse and venereal disease.

The "pretty little things" in the luncheon line, each a member of the California Medical Association Woman's Auxiliary, do all of these things and more.

"When I joined in 1950, the Auxiliary was a social organization," said Mrs. Ward L. Hart of San Carlos, now its president.

"We did some good things; we raised money

for nursing scholarships, for instance, in the usual ways—fashion shows and house tours. And we sponsored health career clubs in high schools.

"Now there has been a tremendous change. We are still social—women still like to get a sitter and go out to lunch. But now we know we have to give our time to some things that are more important, and we do!"

Mrs. Hart, who is dark-haired, soft-spoken and the mother of four, grows animated when she discusses the many and varied things the doctors' ladies are doing in their own communities and over the state. As do many other doctors' wives, she has her own individual project in addition to her work with the Auxiliary. She spends a good deal of time helping with a Head Start program in Redwood City.

This in a way reflects the attitudes and philosophy of the CMA itself—a willingness to consider and accept change, and an awareness of the strong social forces which affect not only the lay communities but the practice of medicine as well.

The Auxiliary members have embarked on programs which, as Mrs. Hart explained, were well outside of their sphere of interest only a few years ago.

"Mission Possible"

In San Francisco, for example, the local medical society's Auxiliary is active in "Mission Possible," a program that works with young people who are school dropouts or close to the dropout point.

St. Luke's Hospital is a cooperating member of this project. The high school students in-

The author, a staff writer for the San Francisco Examiner, has covered medical conventions for that paper and for the *Call Bulletin* which merged with it.

Reprint requests to: CMA Woman's Auxiliary, 693 Sutter St., San Francisco, Ca. 94102.

volved go to the hospital to work part time at jobs for which they are given credit at their schools. But more important than that is the effort to kindle their interest, to give them reasons to go on studying in order to qualify for permanent activity in the health-service field.

Admittedly, it has not worked for all of them. But each single youngster who gains imagination and ambition through this project is a major plus for those who are working to make it succeed.

Ecology—the word which entered the vocabularies of most of us only recently—identifies another area in which members of the Auxiliary are active. The Stanislaus and Monterey-San Benito county wives have made this one of their prime interests. The Stanislaus group assists the Modesto Ecology Action Educational Institute in numerous ways—helping financially, in public relations and in providing volunteers to encourage the recycling of waste materials such as bottles and tin cans. A past president of the county auxiliary handles the programming of a ten-minute weekly ecology spot on the local cable TV station. The Monterey-San Benito members have exerted pressure (never under-estimate the power of a woman) to reduce the air pollution caused by several big industrial plants in their areas.

Anti-drug campaigns occupy many of the county groups; Auxiliary members belong to coordinating boards on drug abuse in Fresno, Sacramento and Stanislaus Counties.

The doctors' ladies don't seem to stop anywhere. "The big statewide push now is the campaign against venereal disease," Mrs. Hart reported. "The CMA is spearheading it, and we are helping in every way we can." The Los Angeles Auxiliary, for example, with the Los Angeles County Medical Association, recently conducted a symposium to educate the educators responsible for communicating the necessary information to the young people who are most at risk. Many other counties are getting started on similar programs, working in close cooperation with the schools. The San Mateo auxiliary provides qualified speakers upon request from schools and interested groups. The belief here is that accurate information is the best kind of insurance for those who might otherwise fall victim to these formidable afflictions.

In still another field, would you believe 1,796,-852 Betty Crocker coupons?

The Auxiliary did it. Coupons from General Mills products, redeemable at the rate of one-half cent per point, were collected in every county in the state, for a program of life-and-death significance to many.

It made possible the purchase of two renal dialysis machines, for areas of need which were determined by the Scientific Board of the CMA. One has been placed in the San Joaquin General Hospital in Stockton, the other at Greater Bakersfield Memorial Hospital, Bakersfield. Additional coupons were sent to the Sacramento Auxiliary to assist them in their effort to collect enough coupons to provide two kidney machines which have been installed in Marshall General Hospital, Placerville, and Sutter Memorial Hospital, Sacramento.

"We really take pride in this," Mrs. Hart said.

Help for Stroke Victims

A task called "Project Re-Entry" is one designed to offset the cruelties of strokes. It was inspired in part by the courage and care which brought about the recovery of stroke-stricken actress Patricia Neal, and is being carried on in cooperation with the federal government's Regional Medical Programs.

The CMA auxiliaries in Los Angeles, Orange and San Diego counties have joined this community effort, recruiting volunteers who are willing to take a course of at least eight weeks to learn the ways in which stroke patients can be helped. Many Auxiliary members themselves are among the volunteers.

The aim here is to develop a pool of skilled volunteer workers capable of offering invaluable services to the victims of stroke. Sadly, and too often, these patients can become burdens to their families as well as to themselves. Yet with care and education they may gain not only physical but emotional strength.

Some members of the families of stroke victims have enrolled in the training programs, to gain better understanding of the problem and greater know-how with which to deal with it. Others are not personally involved, but are public-spirited volunteers with the patience and courage to perform the needed tasks.

To induce a voiceless stroke patient to produce an intelligible word is triumph indeed. This is what the Southern California women are trying

to do—and, indeed, doing. And their pilot project is attracting the attention of others; for example, the Sacramento and Santa Clara county auxiliaries are interested in following suit.

Mrs. Hart feels that this is one of the most worthwhile of the Auxiliary's projects. She recalled one man who was close to emotional as well as physical defeat after a stroke, but who was encouraged to visit an activity center organized by the Auxiliary in conjunction with the RMP. It was designed to "get the patient out of the house and doing something," Mrs. Hart explained, and in this case, among others, it succeeded. Now this man and his fellow stroke victims want to run the place themselves, she reported. That adds up to success.

Health Careers Recruitment

There's a good deal more. The county auxiliaries are at work, for example, on health career programs designed to attract more young people into the often manpower-short medical services.

The doctors' wives raise money for scholarships for young people interested in medical careers. Further, they put on "Health Fairs" for high school students, showing them what kinds of jobs exist in the field of health.

This works both ways, Mrs. Hart said. One program may motivate a student to enter a pre-medical course or one leading to such careers as x-ray or laboratory technologist or nurse's aide. Another may show a youngster dreaming of becoming a physician that it's not all that glamorous, and encourage him to seek another occupation instead.

"GEMS" is still another project of the CMA's energetic Auxiliary. The abbreviation derives from the title "Good Emergency Mother Substitute," a project in which young people and the elderly learn or review some of the important principles of baby-sitting.

Many county auxiliaries are conducting these training sessions. The courses include such matters as what to do in case of fire and what information to get from the departing parents—including especially the telephone number at the place where they can be found if needed.

The young and elderly volunteers are told, for example, not to open the door at the ring of the bell, but to inquire first who is there. They are

instructed not to allow anyone to take away a child, even though he or she may claim to be a parent or relative.

They even learn how to change a diaper, practicing on a real-life baby. Many grandparents will admit that the first new grandchild seems incredibly tiny and fragile, although it may be a pound or two heavier than their own long-grown-up offspring were at birth.

In an even more important way, "GEMS" represents the Auxiliary's interest in the problems of today. For example, the program in a number of areas is concentrated on very young teenagers who care for small children in poverty and ghetto areas.

Mrs. Hart's smile turned a bit wry when she discussed another activity of the Auxiliary—a get-out-the-vote effort within the medical profession itself.

Doctors are known to wear themselves out in the service of their fellow men. But in another area of public service—the vote—they can be surprisingly inactive; in one unnamed California county only 30 percent of the MDs and their wives were registered. Everyone was too busy with other things.

So this is another of the Auxiliary's self-imposed jobs—to seek out the medical families which are not registered. Perhaps it's because they have moved, failed to vote in the last general election, or just didn't think about signing up. The idea is to get these people back onto the voter lists so that they can express their views on the issues and candidates when the time comes.

Still another line of activity is in the collection of drugs and equipment from the offices of physicians. Samples left with physicians by representatives of pharmaceutical firms are picked up and delivered to "Direct Relief," a Santa Barbara-based foundation, and to other similar organizations that help needy people. Members of the "Flying 99's," a group of women pilots organized back in the Amelia Earhart days, help transport these drugs to collection depots all over the USA.

There's more? Yes, there's more.

Medical Journal Subscriptions For Students

Auxiliary members are promoting the donation of subscriptions to California Medicine to medical students, with practicing physicians footing

the modest bill. The women feel that the doctor ought to remember when he was a student himself, and felt too often that he was outside the pale, professionally speaking. Again, it is considered that the monthly CMA publication offers the doctors-to-be not only excellent educational material but the most accurate picture of the state organization to which they will very likely belong in the not-too-distant future.

There's still more? Yes, again.

Mrs. Hart had one more project to report—the raising of some \$80,000 in 1971 and probably more than \$100,000 in 1972 for the American Medical Association-Education and Research Foundation.

The AMA-ERF provides funds to medical schools with no strings attached. Medical school deans decide just where the money can be best used. California Auxiliary members take pride in the fact that this state annually produces more revenue for the foundation than any other.

It's done in all the canny ways that women know so well—the community Christmas card sales, Auxiliary-produced cookbooks, a Los Angeles Ad Book that raises over \$17,000 a year,

the organization of bowling leagues and the collection of their proceeds.

There is still the dressed-up lady lunch, with the “pretty little birds” chattering as they wait for the doors to open. But this has become a less and less significant element in the Auxiliary's ever-widening total of interests and, by now, that male science writer is very probably willing to take back that remark he made about canaries.

And now, since this is an article about the Woman's Auxiliary, we will give the last word to a man. Dr. Jean Crum, current CMA president, is well aware of the Auxiliary's many achievements. To help him express his admiration, he calls upon Voltaire: “All of the reasonings of men are not worth one sentiment of women.”

“It strikes me,” Dr. Crum says, “that this observation offers one clue to the Auxiliary's success. In one way or another, nearly all their programs are concerned with helping people who otherwise might be overlooked. In such activities, compassion and an understanding of human needs are essential. These are qualities for which our Auxiliary is well known.”

ANESTHESIA DEATH IN OBSTETRICS

In summary I would like to say that an honest look at maternal mortality would indicate to us that there is still an excessive number of obstetrical patients dying unnecessarily from the effects of general anesthesia. Conservative estimates would say that this figure was about 100 last year. I believe that it is presently impractical to have an anesthesiologist present at every delivery. But for too long it has been general policy that the least trained person in the theater is suddenly instructed to “give the person a little gas” while the delivery is accomplished. Stating that anyone can give a little gas for a short while is like saying that anyone can fly a 747 if he just goes from Los Angeles to Burbank. It is getting off and getting back that is dangerous. It is getting that little anesthesia aboard and off that is dangerous. I believe that it is incumbent upon both obstetricians and anesthesiologists to insure that those persons who take the responsibility for the life of an obstetrical patient during her period of unconsciousness be adequately trained in the relatively simple steps to prevent potentially tragic complications.

—ERNEST P. GUY, M.D., San Francisco
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Government and Medicine

A Review of the California RMP Program

PAUL D. WARD, *Oakland*

AFTER FIVE AND ONE-HALF YEARS of life, Regional Medical Programs in California emerged as the nation's largest RMP, in both program volume and dollar support. The fifth year emerged as this region's most successful year, even though it followed nearly two years of debate and concern at the national level over what the future role of RMP as a national program should be.

During the period of national debate over the program, there was seldom any question of the validity of the original purposes of the program—to make available to the victims of heart disease, cancer and stroke, through the establishment of cooperative arrangements among existing health providers, the latest advances in treatment leading eventually to a single high quality of care available to all. There was a question, however, as to the priority this effort should receive in the allocation of the money that was available for federally funded health programs.

Early 1970 saw the establishment of a relatively firm set of national health goals which indirectly established priorities. It proved difficult for RMP, as an overall program composed of 55 separate regions, to relate immediately to these priorities since the priorities seemed to be aimed primarily at providing care for those deprived of care and essentially emphasized a non-categorical approach. The RMP authorizing legislation was considered by some national figures as too narrow in scope to get at the nation's basic high priority health needs. The 55 RMP regions

had to reassess their position and determine what role, if any, they could play in meeting these newly identified priority health needs.

The fact of the matter was that most of the successful regions were already coping with several of the problems identified in the national health goals. This effort had not received the attention that other aspects of the program had. Subsequently, there was a significant effort on behalf of the program by national leaders of the medical profession, hospital and voluntary association leadership, and members of local RMP advisory groups to make this fact known.

To some, this signified an abrupt change in the direction of the evolution of the program. To those more familiar with the program, however, it appeared only as an added emphasis on one aspect of the program that had been in existence since its inception.

The fact became obvious early in the planning phase that there was maldistribution of services in some instances, and in these cases it was impossible to plan improved services for heart disease, cancer and stroke if there were inadequate basic services. It was for this reason that some of our first projects were non-categorical in nature and tended to serve the basic medical needs of all patients in certain underserved areas. RMP's early efforts in Watts in conjunction with the King Hospital is a case in point.

As these facts became better known and understood, support for the program grew. There was a distinct turnaround in the outlook on funding for the program. Regions had received cuts in their funding a year earlier, but during recent months additional funding has become

The author is Executive Director of the California Committee on Regional Medical Programs.

Reprint requests to: Executive Director, California Committee on Regional Medical Programs, 7700 Edgewater Drive, Oakland, Ca. 94621.

available on a merit basis. The California RMP, to date, has enjoyed a high ranking on the merit scale for the quality of its program and in this year alone has had three increases for a total of better than a 40 percent increase in total program dollars.

The California RMP obtains its policy and program direction from a consortium of health providers, voluntary associations and lay members formed into a non-profit corporation known as the California Committee on Regional Medical Programs (CCRMP). As of this writing, its corporate membership amounts to 27 professional persons, as representatives of various institutions, professional and voluntary associations, to which public members are added to form the regional advisory group. The legal grantee is the California Medical Education and Research Foundation which, in turn, delegated program and policy responsibility to CCRMP. CCRMP sets the goals and objectives and approves program expenditures, thus determining the direction that the program will take. CCRMP has watched with interest the goals set at the national level but, at the same time, has worked to protect the integrity of its own predetermined concepts of what the program direction should be.

The recent past direction of the California RMP can be seen in our report to the RMP National Advisory Council for continued funding for this fiscal year. At that time (first six months of fiscal 1971), we reported that our total project dollars were spent as follows:

	<i>No. of Activities</i>	<i>Percent of Total Dollars</i>
PURPOSE: To increase the		
1) Quality of individual acts of medical care	70	77.3
2) Accessibility of medical care	5	9
3) Availability of medical care	4	.3
4) Acceptability of medical care	1	.4
5) Quality and availability of medical care	3	3
6) Other activities which contain elements of all the above purposes	3	10
TOTALS	86	100.0

The percentages were determined by breaking each project into its various activities, classifying the activity as to what it was intended to produce, and then weighting its cost against the total

project dollar expenditure. Purpose 1 (in the list above), which represents essentially continuing education, training and retraining in their broadest interpretations, is the dominant thrust of the program. This report was subjected to review by a site visit team which reviewed each project, and to further staff review. No question was raised about the validity of this approach.

Although the programs and activities have significantly increased this year, essentially they are built on our early experiences. California RMP, like programs in other regions, began with a heavy emphasis on the development of coronary care units (CCU). Training physicians and nurses to manage and operate the units was the principal RMP function, but consultation and other services were provided hospitals and their staffs in the development of the coronary care units. Certainly RMP was not responsible for all the CCUs that were created, but through the establishment of the statewide CCU committee and the Confederation of Coronary Care Units where data could be collected and standards of care discussed, RMP did have a direct effect upon the acceleration of this service. It was reported that during this period the number of CCUs increased from 11 in 1966 to more than 250 in 1970.

Early in the course of CCU projects, at a meeting in which we were considering ways to strengthen the then operational training programs, the discussion was interrupted by a practicing cardiologist from a small Northern California community. He said the training programs were good and seemed to accomplish their goals, but an essential point was being overlooked. In his hospital, he said, the chief virtue of CCU training was a boost in morale throughout the whole nursing staff and a decided increase in activity of all the in-service teaching.

The same kinds of reports came from other hospitals as well. And, as the program continued, other benefits were seen. The primary target was training, but regionalization of the training programs made it possible to compare all CCU work, shore up weak points and exchange experience on successes. Finally, what started as a practical manpower training application of advanced research in the care of heart disease led to providing information and putting it back into the channels of research for others to pursue. The cardiologists who directed our CCU training projects were able to set in motion

research, not carried out by us, into the most effective ways of treating myocardial infarctions.

The ccu experience led to the development of one of the region's most sought after training experiences which was descriptively entitled, "The Training of Physicians in Eleven Skills of Intensive Care." Carried out under the aegis of Pacific Medical Center and UCSF Medical School, the program provides on-site training, electronics consultation, electrical safety, acute care nursing and other related matters. As the program develops, more of the training is being accomplished at the local level and, as in the case of ccu training, it is hoped that the major portion will be assumed by community hospitals and colleges.

Our efforts in improving cancer care did not materialize as rapidly as did the ccu program. There were at least two major reasons for this. First, ccus were at a technological stage capable of rapid expansion and, therefore, received early attention. Second, just as the cancer planning was gaining momentum, funding for the program diminished. Nevertheless, during the dark days of funding possibilities, there were several activities in cancer care improvement undertaken. They consisted of clinical cancer consultation services to outlying hospitals, radiological physics services to assist local radiotherapy services, a computerized data retrieval system for patient records and follow-up, and other ongoing training programs. There is need for further regionalization and improvement of services and it is hoped that funding will become available to achieve these ends.

Efforts in the category of stroke have been directed largely toward the development of stroke treatment and rehabilitation teams. Efforts to develop data collection on stroke victims have been carried forward concomitantly, and in one part of the state there is a strong drive to regionalize stroke rehabilitation services in extended care facilities by use of the mobile rehabilitation team. How to continue the impetus for these services after the expiration of RMP funds remains a perplexing problem, but out of this effort there has emerged the drive to create the United Stroke Association, a national non-profit foundation financed from private sources with the goal of drawing greater national attention to the stroke victim. We believe, from our brief

efforts, that mortality rates can be significantly lowered and that through a systematized selection process, intensive rehabilitation pays dividends. This has led to a volunteer training program in stroke resocialization designed to help the discharged stroke patient readjust to his community involvement.

A number of small projects were developed during this period aimed at continuing education for professionals in a variety of disease categories. Kidney disease was added to the Regional Medical Program by Congress during the recent extension of the program. A regionwide committee was developed, composed of leaders in the renal disease field, whose stated purpose was to develop a fully regionalized program. Projects were begun to improve and assure equal distribution of renal dialysis capabilities, to increase transplantation capabilities, to collect and store organs, and to improve the use of available drugs. Also, an information and patient registry system design was begun. It appears that the development of treatment in renal disease is at a point where complete regionalization could be accomplished more easily than with most disease categories.

Also, programs have been developed to increase physician knowledge about chronic respiratory disease. Aimed at improving skills in diagnosis, management and treatment as well as a better distribution of the service, an extensive evaluation effort is planned. Like renal disease, the respiratory disease efforts are of recent vintage, at least as to funding. Other programs have been devoted to information and referral services for patients who have special problems in order to reduce the time and effort entailed in random searching for help. Medical audit programs have been organized to aid community hospitals in developing a means to assess the quality of patient care and thereby assess the educational needs of staff and personnel. Comprehensive programs for neonatal care have been set up, and at least partially funded, for the purpose of reducing neonatal mortality through a systematic method of identifying high-risk patients and the use of physiological monitoring during the perinatal period. Several programs designed to regionalize and upgrade emergency medical services have been developed and are awaiting funding.

In addition, several small programs have been formed to bring services to areas that are underserved medically. The Fresno County Medical Society, jointly with RMP, developed a program to bring services to the Mendota-Firebaugh area in western Fresno County. Since RMP cannot provide direct patient care funds or services, means had to be found to cover service costs outside RMP resources. RMP provided the planning resources and the management capabilities, and organized the delivery system. The California Medical Association contributed \$10,000 early in the planning stage to get the project under way. The services should become available later this year. Other rural clinics have been established, especially to provide services for remote Indian tribes and other isolated groups, where means could be found to pay for the services. All in all, RMP has spent relatively few program dollars on this kind of effort, but staff and study time has been considerable because of the complicating problems of community concurrence and service financing.

Since the beginning, California RMP has been engaged in creating consortiums of health manpower education. This is simply the drawing together of existing efforts in the health manpower training area, comparing the existing effort with the total need and attempting to fill in the training gaps by creating new training

programs. Put another way, it is an attempt to systematize the rather sporadic training efforts that are characteristic of the health field. When the concept of Area Health Education Centers (AHEC) was unfolded as a national health goal, it was obvious that RMP would serve as a natural catalyst for their development. During the past year, California RMP has led the way in AHEC planning. These are designed as community based consortiums which will have the ability to assess the actual need for manpower and have the capability to fulfill these needs through existing institutions.

In summary, although our target groups may change slightly from time to time and old concepts are sometimes called by new names, the process remains the same. The national legislation for Regional Medical Programs, plus the initial planning for its activities in California, have been based on the premise that the best way to achieve success is through a process of regionalization. CCRMP reaffirms this position. Regionalization is achieved through cooperative working arrangements among various available health resources resulting in the maximum quality and quantity of health programs in a defined geographical area. The basic ingredients of regionalization are involvement, identification of needs, assessment of resources, definition of objectives, setting of priorities, implementation and evaluation.

STAGING OF PROCEDURES FOR EAR DRAINAGE

I would like to make one brief plea that reconstructive procedures in the ear be staged. I think that we are at the crossroads now as to whether we should have a one-stage or a two-stage procedure for a draining ear. I would like to associate myself in the strongest possible terms with the man who says, "Let's do the least possible surgery that we can do to get rid of the infection, wait six months, and then rebuild with what we have left." I can't stress this too much; the number of severe crippling cholesteatomas that we see in musculoplasties, old musculoplasties, and old tympanoplasties causes a very great deal of concern. So let's get rid of the infection first and then reconstruct the ear.

—FRANCIS A. SOOY, M.D., San Francisco
Extracted from *Audio-Digest Otorhinolaryngology*, Vol. 4, No. 5,
in the Audio-Digest Foundation's subscription series of tape-
recorded programs. For subscription information: 1930 Wilshire
Blvd., Suite 700, Los Angeles, Ca. 90057

A Special Report

The First Twenty Years of Audio-Digest

CLARON L. OAKLEY, M.S.J., *Los Angeles*

WITH A \$10,000 LOAN (repaid in full by the next year) and the prestige and blessings of its good name, the House of Delegates of the California Medical Association launched the non-profit Audio-Digest Foundation nearly 20 years ago, outlining its long-range goals as follows:

"... To engage in the primary activity of making financial contributions to medical education and other purposes that promote the science and art of medicine, the protection of public health, or the betterment of the medical profession, through the proceeds received from the sale of recorded medical lectures and literature, and the machines and appurtenances thereto used for playing and transcribing said recordings . . ."

In the year preceding its acquisition and sponsorship by the CMA, Audio-Digest operated as a private enterprise, launched from a basic concept envisioned by incumbent California U.S. Congressman Jerry L. Pettis (then employed as Southern California public relations representative for the CMA).

At the end of the first year, it became increasingly doubtful that Audio-Digest would ever thrive as a profit-making, lay-owned and operated enterprise. What was needed, founders Pettis and Oakley concluded, was an air of spontaneity in at least portions of each program; a continuing change of pace in the voices; and, most of all, the electric "you-are-there" feeling that could come from carefully selected and edited on-the-spot recordings of major medical meetings.

Recognizing that a lay-operated, profit-motivated operation could not expect to obtain recording privileges at national medical meetings; and, if it could, that participating lecturers would be unwilling to donate their talents and time without a compensating honorarium or royalty, it was concluded by all concerned that the only solution lay in receiving the kiss of organized medicine on Audio-Digest's brow.

To that end, the CMA was offered and accepted ownership of the then-experimental form of continuing education; and a new kind of electronic medical journalism received the financial and professional impetus required for its gradual evolution into today's Audio-Video Digest Foundation (a name only recently registered to protect its eventual entry into the field of videotape continuing education).

Audio-Digest's unique and exclusive appeal to the profession at large is its hard-won open-door recording privileges at some 200 national specialty meetings and university continuing education courses. In the early days, most organizations would respond to taping requests with a variant of: "Who wants to share their hard-earned program and speakers with a company whose service could conceivably lull doctors into staying home and never attending a meeting in person?" But, as educators and participants began to realize that Audio-Digest would be carrying only a relatively miniscule portion of a meeting's total proceedings and that the accompanying publicity oftentimes bolstered subsequent years' attendance, rather than reducing it, they began to cooperate in ever-increasing numbers: First, The American College of Obstetricians and Gyn-

The author is vice-president and editor of Audio-Digest Foundation.

Reprint requests to: C. L. Oakley, Audio-Digest Foundation, 1930 Wilshire Blvd., Suite 700, Los Angeles, Ca. 90057.

ecologists, then the American Medical Association, and one by one the American College of Physicians, American Society of Anesthesiologists, American Academy of Ophthalmology and Otolaryngology, American College of Surgeons, as well as ongoing refresher courses at such institutions as the Mayo and Lahey Clinics, UCSF, UCLA, USC, University of Utah, University of Michigan, Harvard Medical School, and, eventually, dozens of others.

From several hundred dollars a year for convention recording expenses back in 1954, the annual expenditure for the thousands of convention tapes that now provide the chief reservoir of programming totals several hundreds of thousands of dollars a year.

Which segments of these tapes to consider for inclusion in Audio-Digest is the decision-making crux of our success or failure. Out of the thousands pouring into the Editorial offices from all over the country each year, some are eliminated immediately because of technical failures (line hums, poor microphone placement, public address interference, among many others).

Many are unusable because of their total dependence upon slide material or accompanying movies.

Of the remainder, what to keep and what to relegate to the cutting room floor?

As a starting point, a volunteer staff of specialists in all fields pre-screens the convention tapes, filling out an exhaustive critique on each one, answering such questions as these:

Is the material practice-useful, either in diagnosis or therapy? Is the recording fidelity clear? Is the material truly new, or is it merely a rehash of facts and figures than can be found in any standard textbook? Is the lecture informative, stimulating to listen to, or does he ramble, read his talk in a dull monotone or lull the listener to sleep?

Based on the editors' candid replies to questions like these, a skilled staff of medical tape editors sits down with razor blade and splicing tape to do their crucially-important job of editing. They spend hours cutting out as little as quarter of an inch of tape to spare the subscriber's having to listen to the "uhs," "ahs," throat-clearing, long pauses, and astoundingly bad jokes to which some lecturers subject their original listening audience.

Then, the editor begins looking for those single

phrases, sentences or paragraphs that are extraneous to the subject at hand, weeding out the wheat from the chaff and, in the end, passing on to the Audio-Digest listener a tight, compact, informative lecture that may now take only 10 to 12 minutes to make a point that the lecturer had originally taken 30 minutes to put across. (Naturally, each lecturer is given an opportunity to hear the edited version of his remarks and, virtually without exception, they are amazed when they hear what has been done to condense the highlights of their remarks without doing violence to their message as a whole. As one famed heart specialist wrote after his lecture appeared: "What, you've made me sound almost like Edward R. Murrow or Eric Sevareid. I didn't think it was possible!")

A typical major specialty meeting (e.g., American College of Physicians or American Medical Association annual meeting) can involve as many as 300 speakers, whose permission must be secured before their remarks may be taped and considered for later use. Each of these 300 is sent a personal letter, informing them of Audio-Digest's invitation to tape the session on which they will appear and soliciting their individual cooperation in signing and returning their recording clearance form.

These letters are mailed at least 30 days in advance of the meeting; and, interestingly, at least 95 percent of them are usually returned well before the meeting actually takes place. For the missing ones, staff members make personal contact during the convention, tracking down an evasive speaker who has most often simply forgotten or neglected to sign and return his consent form. In the end, close to 100 percent of the signed permission cards are obtained—but, for those not located; who fail to respond before or after a meeting, or who write to explain that their presentation is "too slide-loaded"; "not applicable to Audio-Digest format"; or "you taped the same material at another meeting"; or who just do not want to be recorded, their remarks are consigned to our erasing machines.

None of the speakers (nor the sponsoring organization) is paid any fee or honorarium for allowing this taping; rather, each has come to feel that they are expanding the walls of the room in which they are speaking and extending their experiences and findings to interested physicians in all parts of the world. Appreciating

that Audio-Digest is a non-profit organization, and that all excess reserves are annually plowed back into continuing education on a national level, they (for the most part) feel amply repaid in the natural ego satisfaction and altruism of knowing that their voice is going from the original meeting site into all corners of the nation and the world.

As for the primary achievement goals the CMA envisioned those two long decades ago, how well, in retrospect, have they been accomplished?

"To Engage in the Primary Activity of Making Financial Contributions to Medical Education and Other Purposes That Promote the Science and Art of Medicine . . ."

Rather than attempting to dole out any "excess" financial reserves at the end of each fiscal year to individual institutions, associations or any of the hundreds of participating professors and clinicians who share so generously of their teaching talents and experiences, the Board of Trustees decided early in the Foundation's history to channel the funds through existing state and national organizations already set up for this purpose.

The American Medical Association's Education and Research Foundation has therefore been a principal beneficiary of Audio-Digest's financial success, with contributions to date totaling just under \$600,000.00. Before consideration of any interest earned by AMA-ERF on these contributed funds, that amount has been sufficient to guarantee loans to worthy and needy students, interns and residents in an amount exceeding \$7,500,000.00. At last report, Audio-Digest contributions had covered loans for more than 2,000 student, resident and intern applications.

In addition to the twice-annual contributions to AMA-ERF, the California Medical Association Education and Research Foundation has also benefited.

Scholarship programs have been established to high school graduates desiring to pursue medical guarantee educations for worthy underprivileged or paramedical careers.

Additionally, to bring the tapes into the daily learning experience of those who can least afford to buy them on their own, gratis subscription programs have been set up for any qualified medical school library in any part of the nation. Typical of the enthusiasm—and broad student

and faculty listening audience that the program has generated—is a letter from the University of Rochester School of Medicine:

"We greatly appreciate the assistance given to us in the Division of Medical Education . . . We feel the tapes have contributed in a most effective way to learning of our clinical students, interns, residents and faculty. We have placed the tapes in the medical library using headphones in one location, and a closed carrel in another, so that regular listening can be utilized. I would hazard the opinion that over one hundred individuals listen to the recordings in any given month, and even that may be conservative . . ."

From the Dartmouth Medical School:

"We have employed the tapes exclusively in educating interns and residents and find them most useful as a take-off point for discussion at our Medical Residents' Journal Clubs, held approximately every three weeks at a staffman's home. A third year resident is responsible for developing a pertinent bibliography and assigning selected references to each resident attending. Thus, each comes prepared to amplify the taped discussion . . ."

From the University of Illinois:

"It helps many a young man and orients him to your form of educational process, giving him valuable current information that's available to him at his particular moment of free time. It serves a very useful adjunct to our training program . . ."

". . . To Engage in Other Purposes That Promote the Science and Art of Medicine . . ."

Thousands of tapes are donated annually to the Medical Assistance Program and circulated to isolated parts of the earth. Executive Director J. Raymond Knighton summarizes the scope and effect of the donated tapes in a recent letter: "My deepest appreciation for the tremendous service you have given to hundreds of our missionary physicians around the world. Your tapes have been the means of updating their techniques and given them a new impetus to serve . . ."

The volunteer staff of "Project Concern," a nonprofit enterprise engaged in donating medical care to refugees, listens to the tapes on a floating hospital ship in Hong Kong's teeming Aberdeen Harbor, then sends them on to the Project's installation in South Viet Nam.

American physicians volunteering for short-

term medical duty in South Viet Nam are being kept abreast of medical developments through donated subscriptions set up through the Military Provincial Hospital Assistance Program. Cavalry Medical Officer Roger A. Jacobs writes: "Am currently in Phao Vinh with three other MD's. We listen together, discuss the material we hear, and look forward to each new tape." Major William A. Bonnefil adds from his evacuation hospital: "The tapes keep me informed of what's happening in Ob-Gyn, especially here in Viet Nam where I don't get a chance to do much Ob or Gyn work!"

A Ford Foundation Population Program Advisor reports: "... the cassettes are being passed on to the Library of the Hospital de la Mujer, Mexico's large charity hospital for women, where they supplement reading assignments for a group of young foreigners who study here, literally from all over the world. Most of these doctors are from developing countries, where a ten year old journal is considered up-to-date. You can imagine that they especially appreciate hearing the current issues of Audio-Digest . . ."

With the goal of helping upgrade anesthesia care and teaching in Latin America, Asia and Africa, subscriptions have been allocated to the World Federation of Societies of Anesthesiologists. From Nigeria, Dr. W. J. Bavington, a recipient of the programs, reports: "In my continuing education here, I give top priority to your tapes. It's so easy to slip into a slipshod type of medical practice where basic examination of the patient and clinical assessment without a full lab is essential. Thank you for your service to the medical profession . . ."

Some foreign physicians come to America with spoken English so poorly understood that they cannot order lunch, let alone understand a CPC or lecture. As a valuable part of their internship training, many an F.M.G. has credited Audio-Digest's taped education with their being able to master pronunciation of not only medical terms, but also day-to-day vernacular.

At the other end of the spectrum—helping the doctor to understand his foreign-language-speaking patient—Audio-Digest is undertaking a pilot program with the CMA Committee on Urban Health to produce an hour-long tape and pamphlet designed to assist the physician cope with the emergency of a Spanish-speaking patient in obvious physical distress.

"... To Engage in the Protection of Public Health..."

A recent Audio-Digest Family Practice program on the control and prevention of Venereal Disease was not only heard by thousands of subscribers, but, by word of mouth, has become an aural handbook on VD and ordered by City and State Departments of Public Health across the nation.

The Bolivian Embassy received permission to duplicate a program on amebiasis to distribute among 15 medical stations in that country, attempting to quash a national outbreak.

A special program on "Pot, Acid and Speed" has been ordered by PTA's, Boards of Education, and physicians from all over the U.S. to familiarize themselves, colleagues, parents, students and general public with the scope of the drug problem.

An exciting example of Audio-Digest's far-reaching impact on the practice of medicine comes in a letter from a ten-year subscriber, Hamilton, Ontario, Internist William M. Goldberg: "... I remember hearing Dr. Belding Scribner discuss the use of chronic dialysis on a tape and was so enthused by his discussion and possibilities that I felt that such a center should be developed in our area. Since that time, and it has taken several years to do this, we have developed a chronic dialysis center for the whole Niagara Peninsula; have eight patients on chronic dialysis; and are rapidly expanding. This sounds a little theatrical; but, quite honestly, the enthusiasm of his discussion (which I am sure I wouldn't have been able to capture had I just read an article) played a great part in the decision to tackle this difficult area . . ."

Dr. John W. Pender (a long-time Trustee of Audio-Digest and instrumental in the establishment of the Anesthesiology series) also notes the impact Audio-Digest has had on clinical medicine: "Whether we like it or not, Audio-Digest bears part of the responsibility of the norm, the standard, and the quality of medical practice. Since 1968, when I spent some time at the University of Pennsylvania, where blood gas determinations were available in the operating suite, I have been advocating such an arrangement . . . The evidence in the latest issue on "Management of the Trauma Patient"—that leaders such as the members of this panel consider blood gas deter-

minations necessary for logical treatment of shock—will undoubtedly promote installation of such facilities in institutions which, up to now, have been dragging their feet. This responsibility is not one we should regard lightly, but, on the other hand, is one that we must pursue boldly.”

“... To Engage in the Betterment of the Medical Profession”

When the CMA adopted Audio-Digest, subscriptions were numbered in the several hundreds. Today, with an average audience of four physicians per individual tape, more than 150,000 physicians all over the world hear each month's issues. This represents enough magnetic tape to stretch between Los Angeles and New York 17 times or to circle the globe twice.

While California was the birthplace of Audio-Digest and represented the bulk of the beginning subscriptions, the greatest concentration of listeners has now shifted from the Far West to states east of the Mississippi river. Sixty-one percent of all subscriptions go to physicians in the Eastern area of the country. More than three percent of all subscribers are now in Canada and assorted foreign countries.

Hospital subscriptions were virtually unknown in the early years. Today, more than 1,000 American and foreign hospitals—totaling some 2500 subscriptions—utilize the recordings in their libraries or training programs.

At the time of the CMA adoption, the number of services offered by Audio-Digest was limited to Family Practice. In January, 1954, Surgery was introduced, followed consecutively by services for Internal Medicine (March, 1954), Obstetrics and Gynecology (April, 1954), Pediatrics (January, 1955), Anesthesiology (January, 1959), Ophthalmology (May, 1963), Otorhinolaryngology (September, 1968).

In midsummer, it is contemplated that the ninth subscription specialty service will be launched—this one, Audio-Digest Psychiatry. Even though initial announcements of this intention have only just recently been made, hundreds of the nation's 20,000-plus psychiatrists have already indicated their wish to subscribe when the service is ready.

(Also after June 30, 1972, a long-time goal of having a single lower rate for both open-reel and cassette versions of Audio-Digest will be realized: \$75.00 a year for 24-issue subscriptions in

either listening modality. Most of Audio-Digest's imitators charge that same rate—or more—for only half as many issues.)

Comparing the number of physicians in office-based practice with their counterpart number of Audio-Digest subscribers, the most recent survey indicates this remarkable saturation of the available market: 41.05 percent of all Board-certified Anesthesiologists; Ophthalmologists, 35.80 percent; Otorhinolaryngologists, 32.25 percent; Internists, 30.32 percent; Pediatricians, 29.93 percent; Obstetricians and Gynecologists, 25.55 percent; Surgeons, 23.36 percent; Family Practitioners, 18.26 percent.

In addition to the specialty programs in the eight series listed above, special six-cassette “Short Course Albums” have been introduced, broadening even further the Foundation's spectrum of educational coverage for the entire medical profession. Recent albums include such titles as “Office Gastroenterology,” “Diagnosis and Treatment of Cancer,” “Cardiology,” “Respiratory Therapy” and an upcoming series in “Urology.”

For the fiscal year ending June 30, 1971, Audio-Digest management had set an ambitious goal of reaching an annual growth rate of 17.5 percent. Not only was that goal met, but it was exceeded by some seven percent, with total subscriptions increasing by nearly 25 percent during the 12-month period. (A percentage even more impressive when compared with the growth rate of the U.S. physician population of $-.1$ percent during the same period.)

During that same period, renewals for all eight services soared to a collective high of 81.18 percent. Seven of the eight services reached 80 percent or higher in renewals; and three of them succeeded in reaching a virtually unreachable goal in publications circles of 90 percent renewals. (The champion renewal rate holder among lay publications is “Readers Digest,” with 75 percent; and most weekly “slicks” are satisfied to reach the halcyon goal of 70 percent repeat business.)

An increasing number of state and national specialty societies are laying down stiff continuing education requirements as a physician's price of membership. Many medical societies—including two of the largest, California and Oregon—include Audio-Digest listening in their categories of media that qualify as “Required.”

Back issues of Audio-Digest programs (ordered from a Catalog of Classics, available on request) are reportedly helping many physicians prepare for (and successfully pass) their national Board examinations, as well as qualifying for high scores in their specialty's ongoing self-evaluation assessments.

"I recently took the ASA Self-Evaluation Examination," Spokane physician Richard L. Pokorny writes, "and my score was in the higher percentile. I credit Audio-Digest for much of the up-dating I have been acquiring and feel it is the source of most practical information." And a New Jersey surgeon, in recently preparing for the American Board of Surgery examination in another city, reports: "Commuting over the 3-week period required 30 hours of driving. During this time, I listened to the entire last year's Audio-Digest subscription. Your tapes were better than the course and were a very significant contribution to my passing the examination. When asked a question, I would very frequently mentally switch on one of your tapes and thereby render a coherent, organized answer to the question."

A plan to stimulate group study in California community hospitals—building the discussions around selected Audio-Digest programs—is presently being carried out under the guidance of Phil R. Manning, M.D., USC Postgraduate Education head and an Associate Editor of Audio-Digest.

"A group of 30 physicians in the Antelope Valley have listened to the tape on low back ache and the one on abortion," Dr. Manning's inaugural report states. "Prior to that, one of these members reviewed the tape and was thereby prepared to lead a group discussion. Following this, a long distance telephone call was made to an appropriately-qualified SC medical school faculty member and the conversation and questions between the group and our faculty man carried out via speaker phone. The initial response makes the method look promising . . ."

In recent years, to expand even further the horizons of Audio-Digest's "listening" audience, CALIFORNIA MEDICINE has published as bottom-of-the-page fillers selected nuggets and pearls from the taped programs—e.g., "A rule of thumb for antibiotic ototoxicity"; "On-the-spot treatment of burn injuries"; "How to evaluate noisy breathing in infants."

Several years ago, we became aware that the American female physician was one of our most dedicated brands of listener, because of the special ways that the tapes benefited someone who was also simultaneously a wife, mother and/or homemaker, in addition to maintaining a practice. Among the typical clues in daily correspondence:

"I most enjoy the fact that I can listen while doing boring but necessary things about the apartment: washing clothing, drying my hair, bathing, sweeping the floor or mending." Or another one: "I listen primarily in the kitchen while cooking or cleaning up, in between chasing three pre-school children . . ."

It was decided to sample promote a specific mailing to female physicians, even though they represent only 7 percent of the total physician reservoir. The mailing—hot pink envelope, long-lashed pseudo-physician models and all—was a smashing success, both in numbers of new subscriptions received and in the warm response from distaff physicians flattered at the special attention to their needs.

Wrote one: "I've been considering Audio-Digest for some time, but was finally persuaded to begin now by the attractive ad aimed specifically at me and my colleagues. The first I've ever seen; and it's nice to know someone knows we exist."

(Just one sour-note letter arrived from a Manhattan Woman's Lib spokesman, who called the mailing "offensive, patronizing and insensitive.")

While doctors in Australia have subscribed to Audio-Digest in small numbers over the years, our surveys indicated that the majority of the profession "Down Under" was unaware of our existence. This has also changed in the past year with a mass mailing to Australian specialists, resulting in a heavy response of new subscriptions from Sydney, Melbourne, Canberra, Perth and hamlets in isolated corners of the huge nation's rugged outback country.

Due almost solely to the crusading missionary zeal of an enthusiastic Anesthesiology subscriber in Belgium, who holds regular group sessions where he plays portions of the tapes and then signs up the Common Market physicians en masse, our Continental Europe subscriptions have also boomed significantly in the past 24 months.

Two other sales representatives are in Japan

and one in Canada (all working on a straight commission for subscriptions booked) and are aiding in making Audio-Digest a truly international service, far removed from the purely-California provincialism of its early years.

The highways of tape journalism are already littered with the skeletons of tape-recorded projects meant to imitate the remarkable success of the Audio-Digest Foundation, but which somehow floundered and died before reaching their destination. The decedents are not only found in all specialties of medicine, but in a host of other non-medical specialties, as well.

Why has Audio-Digest thrived while others have fallen at the wayside in such numbers?

Among the more obvious answers: It is not profit-motivated, but service-motivated; it is owned and operated by physicians for physicians; It has, because of its ownership by organized medicine, an exclusive entree to avenues of continuing education that are barred to those who would exploit the system for sheer capital gain. And, most importantly of all, it is fulfilling a definite need in the continuing education demands of both the busy urban and rural practitioner, be he a specialist or a generalist.

Nearly one-quarter of Audio Digest's new subscriptions come in "over the transom"—i.e., not as a result of a promotional piece received in the mail, but, most likely through the word of mouth of a colleague who has enthusiastically endorsed the program. From our continuous ongoing surveys—but, most specifically, from the daily influx of unsolicited mail from subscribers themselves—the reason for this enthusiasm lies not only in superior programming, but also in the fact that the tapes help him to get double-duty from otherwise-wasted time:

"I keep my tape recorder at the office and listen to parts of tape during lulls in activity" . . . "Have a small recorder on my desk and, after dictating morning correspondence and before appointments begin, I listen." . . . "Living in Florida, I find they are most useful when sun bathing. That's a time when reading is impractical—and the tapes time the length of exposure." . . . "I travel daily from the North side of Chicago to the near Westside on the el. While other passengers are reading the newspaper, I usually listen to the tapes." . . . "I have an Exercycle machine which I ride each evening for 15 minutes. Next to it, I have my recorder and thereby exer-

cise both my body and my mind." . . . "Tuesday evening, I always go to the office to read and listen to my tapes. It's my night to keep up." . . . "I find the most satisfactory time to listen is while I'm shaving and getting dressed in the morning. Since five to ten minutes a day is all that's necessary to complete one issue before the next is due, there's really little problem in finding the time to listen."

There are even more exotic and unusual methods frequently reported: "My tape recorder is equipped with an oscillator (a small transmitter) and I can pick up the sound on my transistor-broadcast-portable receiver anywhere in the house or nearby vicinity. I can work in my garden and listen at the same time." . . . "Listen while I sit on the toilet and other such earthy times." . . . "I run three miles a day. While jogging, I listen to Audio-Digest on a 3-pound recorder strapped to my back." . . . "I row every morning before breakfast. I can go through one tape in a week." . . . "I listen while I'm at the barber every Friday." . . . Or, perhaps the capper of them all, "I listen while bowling—but it's a little hard to hear above the ball-and-pin clatter!"

From the early days on, Audio-Digest was promoted as a means of converting wasted auto travel time into a period of productive learning. The rub lay in the fact that the smallest recorders available weighed some 44 pounds (too heavy to lug in and out of the car); they played cumbersome reel-to-reel tapes that were difficult to reverse while traveling; an electrical converter was required to operate the recorder; and parts and installation, plus the cost of a subscription, could run well in excess of \$500 to put the doctor into a car-listening situation.

All of these cumbersome and economic handicaps disappeared, however, with the introduction of Lilliputian-sized recorders and the invention of cassette tapes. Simply speaking, the recorded tape is encased in a plastic container scarcely larger than a pack of cigarettes and snaps in and out of the recorder with no need to handle the tape itself.

Today, nearly 90 percent of Audio-Digest subscribers subscribe to the cassette, rather than the reel-to-reel modality; and the upshot is that car listening is more popular than ever before.

At least one vehement non-subscriber has angrily inquired: "Why, with so many accidents and deaths on the highways, do you suggest lis-

tening to tapes while driving?" But we have yet to hear of a subscriber fatality or even minor accident due to his being absorbed in listening to a tape—and, if he were, he is just as likely to be distracted by listening to the 6 o'clock news on his car radio. As one subscriber substantiates the relative safety, "I travel 40 miles daily to and from my hospital and listen to the tapes en route. This ride used to be a frantic scramble at 60 to 80 miles an hour to 'save time.' Now, I sit back and relax and drive at around 50 mph. I feel safer, as well as better-educated."

There are others—the majority of Audio-Digest listeners, in fact—who choose more traditional and quiet locations for their weekly or bi-weekly absorption of the taped material. Their viewpoint is perhaps best expressed by Subscriber John J. Stern of Utica, N.Y.: "I pity the poor slaves who have to partake of some of the finest food for thought while they jog, shave or have breakfast. When I exercise, I want to enjoy the satisfaction of feeling my body function smoothly. When I shave, I want to organize my thoughts for the day. And, when I breakfast, I want to

talk to my wife or look over the morning paper. Anybody who cannot afford the time to listen to the tapes in leisurely comfort, making some notes and storing the wealth of information without outside interference, should have his life examined . . ."

Speaking to the physician who complains of "too little time" to keep up with his tapes, Subscriber James H. Maroney of Summitt, N.J., perhaps says it all: "Remind him that the tapes are about a year ahead of anything in print and rank first among all postgraduate education courses. Anyone who can't keep up with every-other-week tape arrivals is neglecting other, and probably all, forms of postgraduate education—and he'd better change his ways and budget his time."

And, whether referring to Audio-Digest or to any method of continuing education, Joseph Lister's cogent comment to the reluctant learner: "You must always be students—learning and unlearning till your life's end. And if, gentlemen, you are not prepared to follow your profession in this spirit, I implore you to leave its rank and betake yourself to some third-class trade."

From a Medical Student

Health and the Low Income Family

JOHN L. GANGITANO, B.A., *Sacramento*

THE PURPOSE OF THIS PAPER is to present what I believe to be some of the most important issues involving the delivery of health services to low income families. The information in this paper is based on my personal experiences in working with the migrant workers' program in Yolo County. The topics briefly covered include fee-for-service health care, physician-patient relations, fragmented health care, and recommendations for improvement of the delivery of health services to low income families.

Fee-For-Service

One of the major problems I found to be present while working with low income families had to do with the delivery of health care on a fee-for-service basis. The poor, by definition, lack adequate finances, and often find themselves unable to remedy health needs because of the high cost of medical care. There appears to be a bias against low income families when health care delivery is based on a fee-for-service system; this assumption is supported by a recent survey of Yolo County (Tables 1 and 2). The Yolo County survey revealed that there was a progressive increase in the expenditure on care provided by a physician, number of physician visits, and number of dentist visits per household that closely correlated with the level of a family's income and socioeconomic status. As would be expected, many low income families were not

visiting a physician due to the necessity of their having to pay for the health care they received (Table 3). This data emphasizes the inequalities that may exist in health care delivery based on a fee-for-service system.

With a fee-for-service health care system, the current high cost of medical care, and a general tendency of private practitioners to work in high socioeconomic and suburban areas, low income families cannot afford and are usually deprived of the level of medical care enjoyed by higher income families. In order to establish a program as an alternate to a fee-for-service system and to provide adequate health care in low income areas, the poor must become involved in planning health care delivery programs; this would act as a balance to the self interest of the professions and tendency toward under-financing of health programs by local government. The combined efforts of physicians, the government, the poor, and a large portion of the public must be enlisted in the struggle to overcome the present inequalities of a fee-for-service health care delivery system if we are to be successful in providing adequate health care to low income families.

Physician-Patient Relations

It has been my experience in working with migrant laborers that it is often a feeling of friendship for the physician that is more important in keeping the patient returning to clinic until treatment is completed than the physical problem the patient is experiencing. As with all

The author was a fourth-year medical student, Class of 1972, University of California, Davis, School of Medicine, at the time this report was submitted.

Reprint requests to: J. L. Gangitano, M.D., 915 Johnfer Way, #11, Sacramento, Ca. 95831.

TABLE 1.—Mean Number of Physician and Dentist Visits a Year per Household by Adjusted Income*

Adjusted Income (\$)	No. of Households Surveyed	Mean No. of Physician Visits	Mean No. of Dentist Visits
<1000	99	5.0	0.9
1000-1999	108	7.7	3.1
2000-2999	183	8.4	3.6
3000-4999	313	9.9	3.7
5000-7499	209	10.0	3.8
7500+	141	9.0	4.5

*1. Adjusted income=Household income
Adjusted family size

a. Adjusted family size:

The first adult (i.e., husband) counts as 1 person.
The second adult (i.e., wife) counts as 1/2 a person.
The third adult (any family member over 16 years old) counts as 1 person.

Children under 16 years old count as 1/2 a person.

2. This table was compiled from the 1970 Yolo County survey.

TABLE 2.—Total Net Expenditure per Household per Year by Socioeconomic Status (SES)

SES*	Physician Expenditures (\$)	Number Surveyed
0	81.3	54
1	98.5	84
2	115.9	163
3	156.6	207
4	135.0	140
5	183.3	129
6	176.1	105
Mean/Total	141.9	882

*S.E.S.=education + occupation + income

1. 0 points for:

- a. less than a high school education
- b. semiskilled or farm labor, students, housewives, retired
- c. income less than \$3,000

2. 1 point for:

- a. some or completion of high school
- b. clerical work, sales personnel, technical, administration, management
- c. income between \$3,000 and \$9,999

3. 2 points for:

- a. some college or more
- b. profession
- c. income \$10,000 or more

physician-patient relations, the patient's emotional make-up and his cultural mores have to be considered in order to properly treat his physical ailment.

The migrant workers that came to our clinic wished to be treated in the same courteous manner that you or I would expect while visiting a private physician. I have been told by a health aide that migrant workers will test health care facilities: first they will bring their child to a clinic and if they think the child was treated well, when the mother needs care, she will come to the clinic; if they think she was treated well,

TABLE 3.—Has Spending Money Ever Kept You From Seeing a Doctor?

Income*	Percent Answering Yes	Percent Answering No	Total No. of Households Surveyed
<1500	46.7	53.3	70
1500-2999	40.1	59.9	72
3000-4999	46.2	53.8	105
5000-7499	47.5	52.5	165
7500-9999	35.1	64.9	138
10,000-11,999	34.0	66.0	133
12,000-14,999	31.5	68.5	134
15,000-19,999	28.5	71.5	109
20,000-39,999	8.1	91.9	60
40,000 +	0.0	100.0	7

*1969 income of household before taxes in Yolo County

when the father needs care, he will come to the clinic. A bad impression on an early visit, then, could result in inadequate health care follow-up of an entire family.

Frequently the professional detachment that physicians maintain in dealing with their patients suggests to the patient a lack of personal interest or concern for him. This is a misunderstanding that unfortunately prevails among poor people in dealing with physicians; it must be corrected by a physician's action rather than words. No matter what we do to improve health care facilities for the poor, there will be little utilization of these facilities if there is an impression of minimal concern on the part of physicians and ancillary personnel for the people they are treating.

In order to bring about greater personalization of health services, health aides indigenous to the population being treated must be utilized, as they have been employed in working with migrant laborers in Yolo County. The presence of a peer acting as a health aide relieves some of the patient's anxiety and allows the physician greater insight into the patient's problems.

After having visited a number of migrant workers' residences with crowded living conditions, central toilet and bath facilities (often for six or more families), and plywood partitions separating bedroom from kitchen, it was apparent that a physician's knowledge of a patient's illness coming from such an environment is not enough: the physician must know what is going to be done about the patient's problem when he sends the patient home with a prescription or orders to be followed; for example, I recall a patient

who was told to shower or bathe three times a day by a physician who did not know there were no bathing facilities in the patient's home. Knowledge of the environment from which a patient comes is an important part of physician-patient relations, and I have found it of particular value in dealing with low income families who often lack many of the modern conveniences that a large number of us take for granted.

The success or failure of not only acute but also preventive health care measures depends to a great extent on the environment in which a patient lives. Often the environment in which the poor are brought up leads not only to lack of health education but also a fatalistic feeling of powerlessness to change destiny—based on life experience. Often this results in unresponsiveness to preventive health services.¹ Often ill health must become serious illness, or interfere with their ability to earn a living before the poor will seek health care.¹ They are too much engrossed with the present to be concerned about the future, and hence may let preventive health needs fall by the wayside.

If physician-patient relations are to be responsive to the health needs of low income families, the powerful influence of their environment and the personalization of health services will play an important role in all physician-patient interactions.

Fragmented Health Care

Most of the migrant workers in Yolo County and many members of low income families are paid on an hourly basis without compensation for time taken off from the job to meet health care needs. Therefore, a visit to a physician during the day means loss of time from the job and a decrease in their already meager earnings. Frequently this loss is compounded by the patient's having to travel long distances to the closest health care facility, having to visit health care facilities at different locations (*i.e.*, laboratory, clinic), and necessitating the need for transportation, which is often not available (Table 4). Thus, the maze that the patient must pass through to reach the goal of medical care may act as a deterrent in itself of the attainment of that goal.

In my opinion, one of the most important steps in eliminating fragmentation of health care is the development of comprehensive health care

TABLE 4.—Was Lack of Transportation a Reason for Not Visiting a Physician?

Income*	Percent Answering No	Percent Answering Yes	Total No. of Households Surveyed
1500	77.8	22.2	72
1500-2999	79.7	20.3	74
3000-4999	81.1	19.9	106
5000-7499	91.8	8.2	171
7500-9999	93.0	7.0	142
10,000-11,999	96.3	3.7	135
12,000-14,999	99.3	0.7	136
15,000-19,999	97.2	2.8	107
20,000-39,000	98.4	1.6	62
40,000 +	100.0	0.0	8

*1969 income of household before taxes in Yolo County

centers that are easily accessible to low income families. These centers minimize health care time expenditure and decrease time lost from the job. Much has been done in Yolo County to eliminate fragmentation of health care delivery by the creation of clinics based in migrant camps. These migrant camp clinics have mobile laboratory facilities and are staffed by physicians and nurses during evening hours when most of the workers have returned to camp. With such comprehensive health care centers based in low income areas, more low income families can receive the medical attention they need. Meanwhile many low income families will continue to remain with health needs unsatisfied.

Health Care Goals

One of the primary goals of any health care delivery system should be the application of current medical knowledge in an attempt to remedy the health needs of all. We have the ability to successfully treat many health disorders; yet as has been pointed out by the President's Commission on Heart Disease, Cancer, and Stroke, "Many of our scientific triumphs have been hollow victories for most of the people who could benefit from them . . . for the pace of science is bringing more within our reach, but the pace of application allows them to slip through our grasp." It is the low income family that frequently does not benefit from current medical knowledge due to the lack of its application at all levels of society. We must remedy this situation.

Due to the immensity of the problem of delivering health care to low income families,

multiple agencies will be forced to pool their resources to solve it. A number of recommendations were made by the National Advisory Commission on Health Facilities' report to the President in December, 1968, which I believe to be pertinent to the delivery of health care to low income families. These recommendations suggested that efficient health care systems: (1) be organized to insure every citizen access to quality care, (2) should have states, regions, local communities, and all health institutions carrying out continuous planning, (3) should include in the making of decisions both those who provide and those who use health services, and (4) should have interdependency at all levels of health care. Any program that aspires to improve our current health care delivery system must consider these recommendations seriously. These programs will have to be supported by the public in order to be effective. Health is a societal responsibility and society must be prepared to allocate more resources to health if it wishes to distribute personal services to the poor.²

Discussion

All strata of our society must become involved in planning and carrying to completion a health care delivery system for low income families. The inadequacies of a fee-for-service health care

system, depersonalization of physician-patient relations, and fragmentation of health care must be overcome if we are to give low income families proper medical care. The recommendations made herein, *i.e.*, comprehensive health care centers, were meant to serve as suggestions as to methods by which we could improve health care delivery to the economically deprived. With today's high level of medical knowledge and social concern, good health care should not be the privilege of a few; it should be the right of all.

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102nd Annual Session of the CMA

and

Second Western States Invitational Scientific Assembly

March 10 to 14, 1973

Disneyland Hotel

Anaheim

In Memoriam

BAMBAUER, LLOYD S., Porterville. Died February 13, 1972 of cerebral vascular accident, aged 74. Graduate of University of California Medical School, Berkeley-San Francisco, 1932. Licensed in California in 1932. Doctor Bambauer was a retired member of the Tulare County Medical Society and the California Medical Association, and an associate member of the American Medical Association.

**

BARBOUR, NATHAN POWELL, Lockeford. Died November 29, 1971 in Stockton of generalized arteriosclerosis, aged 85. Graduate of Hahnemann Medical College of the Pacific, San Francisco, 1914. Licensed in California in 1914. Doctor Barbour was a retired member of the San Joaquin County Medical Society and the California Medical Association, and an associate member of the American Medical Association.

**

BORENSTEIN, MILTON K., Anaheim. Died April 9, 1972 in Anaheim of cancer, aged 52. Graduate of Washington University School of Medicine, St. Louis, 1950. Licensed in California in 1955. Doctor Borenstein was a member of the Orange County Medical Association.

**

GIBBONS, HAROLD M., Sacramento. Died April 2, 1972 in Sacramento of heart disease, aged 56. Graduate of Tulane University School of Medicine, New Orleans, 1941. Licensed in California in 1942. Doctor Gibbons was a member of the Sacramento County Medical Society.

**

HANSSSEN, EILIF CARL, Pasadena. Died March 31, 1972 in Los Angeles of perforated duodenal ulcer, aged 73. Graduate of Columbia University College of Physicians and Surgeons, New York, 1924. Licensed in California in 1946. Doctor Hanssen was a member of the Los Angeles County Medical Association.

**

HARE, DONOVAN ROBERT, Long Beach. Died March 29, 1972 in Long Beach of carcinoma, aged 43. Graduate of the College of Medical Evangelists, Loma Linda-Los Angeles, 1959. Licensed in California in 1960. Doctor Hare was a member of the Los Angeles County Medical Association.

**

MARKS, JOSEPH HERBERT, Los Angeles. Died April 14, 1972 of heart disease, aged 69. Graduate of St. Louis University School of Medicine, 1928. Licensed in California in 1930. Doctor Marks was a member of the Los Angeles County Medical Association.

**

MOVICH, NATHAN, Los Angeles. Died March 19, 1972 in Seal Beach of heart disease, aged 64. Graduate of College of Osteopathic Physicians and Surgeons, Los Angeles, 1932. Licensed in California in 1932. M.D. degree from California College of Medicine, 1962. Doctor Movich was a retired member of the Los Angeles County Medical Association and the California Medical Association, and an associate member of the American Medical Association.

RAND, CARL WHEELER, Los Angeles. Died April 3, 1972 in Los Angeles of heart disease, aged 86. Graduate of Johns Hopkins University School of Medicine, Baltimore, 1912. Licensed in California in 1916. Doctor Rand was a member of the Los Angeles County Medical Association.

**

ROTH, EARLE FREDERICK, Palo Alto. Died April 3, 1972 in Santa Cruz, aged 80. Graduate of Stanford University School of Medicine, Palo Alto-San Francisco, 1920. Licensed in California in 1920. Doctor Roth was a retired member of the Santa Clara County Medical Society and the California Medical Association, and an associate member of the American Medical Association.

**

SANGALLI, FRANCESCO FRANCO, Fremont. Died April 3, 1972 in Hayward of carcinoma metastatic to liver from lung, aged 47. Graduate of Regia Università degli Studi di Pavia. Facoltà di Medicina e Chirurgia, 1949. Licensed in California in 1954. Doctor Sangalli was a member of the Alameda-Contra Costa Medical Association.

**

SCIARONI, GEORGE H., Fresno. Died March 31, 1972 in Fresno of heart disease, aged 80. Graduate of University of Arkansas School of Medicine, Little Rock, 1914. Licensed in California in 1915. Doctor Sciaroni was a member of the Fresno County Medical Society.

**

SICKAFOOSE, HARRY R., San Clemente. Died February 26, 1972, aged 78. Graduate of the Hahnemann Medical College and Hospital, Chicago, 1919. Licensed in California in 1942. Doctor Sickafoose was a member of the Orange County Medical Association.

**

SMITH, PAUL M., San Clemente. Was killed March 10, 1972 near Laguna Beach in a scuba diving accident, aged 52. Graduate of the University of Minnesota Medical School, Minneapolis, 1943. Licensed in California in 1965. Doctor Smith was a member of the Orange County Medical Association.

**

WAYNE, CHARLES M., Gardena. Died November 21, 1971 of heart disease, aged 65. Graduate of University of Illinois College of Medicine, Chicago, 1931. Licensed in California in 1946. Doctor Wayne was a member of the Los Angeles County Medical Association.

**

WILKENNING, RALPH LEROY, Bakersfield. Was killed in an automobile crash near Bakersfield, April 20, 1972, aged 57. Graduate of University of Tennessee College of Medicine, Memphis, 1943. Licensed in California in 1951. Doctor Wilkenning was a member of the Kern County Medical Society.

**

YAKER, DAVID N., Los Angeles. Died March 31, 1972 in Los Angeles of respiratory failure, aged 73. Graduate of University of Colorado School of Medicine, Denver, 1923. Licensed in California in 1924. Doctor Yaker was a member of the Los Angeles County Medical Association.

BOOK REVIEWS

CALIFORNIA MEDICINE does not review all books sent to it by the publishers. A list of new books received is carried in the Advertising Section.

INTRODUCTION TO HEMATOLOGY—Samuel I. Rapaport, M.D., Professor of Medicine, Head, Hematology Division, Department of Medicine, University of Southern California School of Medicine and The Los Angeles County-University of Southern California Medical Center, Los Angeles. Medical Book Department, Harper & Row, Publishers, 49 East 33rd Street, New York City (10016), 1971. 403 pages, 112 illustrations, \$10.50.

Dr. Rapaport has written a book which provides a missing link between the standard hematologic tome and the lecture notes from medical school. It is truly an introduction to hematology, a concise synoptic review of the essentials of practical everyday hematology. This well-written book is not for the hematologist, but for the practitioner, for the house officer and for the student who wants a book which provides a broad basis of knowledge upon which he can build and which includes some basic concepts of practical therapeutics.

The text contains a good deal of basic physiology (for example, leukocyte kinetics) presented in clear, easy to understand prose and the content is up to date, as for example the discussion of the role of dilantin and the oral contraceptives in folic acid deficiency. Congratulations are due to the author and his photographer for producing some of the best black and white photomicrographs of hematopoietic tissues I have ever seen.

All is not superb. The discussion of glucose 6-phosphate dehydrogenase deficiency is a bit sketchy and there is an error in the discussion of the Philadelphia chromosome. The drawbacks are minor. This reviewer believes that the book serves its purpose admirably. I fully intend to recommend it to, and use it for, the medical students I teach—whether they are currently in school or whether they graduated 30 years ago.

LOIS F. O'GRADY, M.D.

* * *

UREMIA—Progress in Pathophysiology and Treatment—John P. Merrill, M.D., Professor of Medicine, Harvard Medical School; Director, Cardiorenal Section, Peter Bent Brigham Hospital, Boston; and Constantine L. Hampers, M.D., Assistant Professor of Medicine, Harvard Medical School; Director, Dialysis Facilities, Cardiorenal Section, Peter Bent Brigham Hospital, Boston. Grune & Stratton, Inc., 757 Third Avenue, New York City (10017), 1971. 115 pages, \$7.00.

It is not infrequent that a physician faces decisions regarding the symptoms, etiology and management of a uremic patient. Over the past one or two decades, tremendous advances have been made in the field of the pathophysiology and treatment of the uremic patient. This field, therefore, is not dissimilar from others in medicine. All of us as physicians admittedly find it difficult to be thoroughly acquainted with all of these advances. This book is a concise succinct summary on the subject of uremia which can bring a physician rapidly up to date on the most recent proposals and observations regarding this entity. It makes no claims of "being all-

inclusive" but each facet discussed is well referenced, allowing the reader to further pursue in detail any facet of particular interest to him.

I am impressed on the excellent current bibliography provided on the subject (nearly 300 references). Most of these references are from current literature dating even into 1970. If for no other reason, this book is excellent to have in one's library for a reference source on the subject.

The book, which can be rapidly read, being only 115 pages in length, is actually an augmentation and updating of material which appeared in the *New England Journal of Medicine* in April of 1970 on the pathophysiology of uremia. The book, however, in addition contains an entire section devoted to the current concepts of treatment of the uremic patient. Not only is hemodialysis, peritoneal dialysis and transplantation discussed, but the initial conservative phase of treatment is also emphasized. Various complications of the uremic patient are also discussed. The book is also well illustrated and contains a number of excellent radiographic reproductions.

I highly recommend this book to any clinician, but particularly to the general practitioner or internist as a very current, concise, well-documented review on the subject of uremia, its pathophysiology and treatment.

ROBERT E. SODERBLOM, M.D.
MILTON G. CRANE, M.D.

* * *

A PRIMER OF CLINICAL DIAGNOSIS—William B. Buckingham, M.D., Associate Professor of Medicine, Department of Medicine, Northwestern University Medical School, Chicago; Marshall Sparberg, M.D., Assistant Professor of Medicine, Department of Medicine, Northwestern University Medical School, Chicago; Martin Brandfonbrener, M.D., Professor of Medicine, Chief of Cardiology, Department of Medicine, Northwestern University Medical School, Chicago. Harper & Row, Publishers, Inc., Medical Department, 49 East 33rd Street, New York City (10016), 1971. 356 pages with 154 illustrations, \$12.75.

This short textbook was developed to meet new curriculum requirements at Northwestern University Medical School, where students are taught physical diagnosis in their freshman year. The basic skills of diagnosis are concisely but thoroughly covered in language which can be understood by students who are in the process of learning human anatomy and physiology, and have not yet studied organ system pathology. The book should prove very useful, not only to students in the kind of curriculum presented at Northwestern University, but as an aid to self instruction for medical students wishing to indulge in clinical work before having had formal courses in physical diagnosis, or as a textbook for use in nursing or other paramedical professional training programs.

ELLEN BROWN, M.D.

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